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Residential Indoor Air Quality Guideline

Science Assessment Document

ACETALDEHYDE

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ACETALDEHYDE

Water and Air Quality Bureau
Healthy Environments and
Consumer Safety Branch

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LIST OF ACRONYMS AND ABBREVIATIONS

ACS	Acetyl-CoA synthetase
ALDH	Aldehyde dehydrogenase
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
CI	Confidence interval
CO_2	Carbon dioxide
dG	Deoxyguanosine
DNA	Deoxyribonucleic acid
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in one second
HEC	Human equivalent concentration
IARC	International Agency for Research on Cancer
I/O	Indoor/Outdoor
LOAEL	Lowest observed adverse effect level
LOEL	Lowest observed effects level
MOA	Mode of action
NOAEL	No observed adverse effect level
NOEL	No observed effects level
8-OHdG	8-hydroxydeoxyguanosine
PBPK	Physiologically based pharmacokinetic
PC_{20}	Provocative concentration at which FEV_1 is reduced by 20%
PdG	N^2-propano-deoxyguanosine
ppb	parts per billion
ppm	parts per million
RD_{50}	Concentration required to reduce the respiratory rate by 50%
RfC	Reference concentration
RIAQG	Residential indoor air quality guideline
sRaw	Specific airway resistance
STGM	Standard error of the geometric mean
TC	Tolerable concentration
TC_{05}	Tumourigenic concentration associated with a 5% increase in tumour incidence
UF	Uncertainty factor
U.S. EPA	United States Environmental Protection Agency
VOC	Volatile organic compound
WHO	World Health Organization

EXECUTIVE SUMMARY

Background

Acetaldehyde is a colourless, flammable liquid with a pungent and irritating odour, volatile at ambient temperature and pressure, and is found in both indoor and outdoor air. In Environment Canada and Health Canada's 2000 *Priority Substances List Assessment Report: Acetaldehyde*, it was concluded that acetaldehyde is toxic under the *Canadian Environmental Protection Act, 1999* (CEPA) because it may be a genotoxic carcinogen; however, there was considerable uncertainty as to the actual cancer risk. Since the publication of the report, a number of key studies have been published, including those related to the mode of action for acetaldehyde carcinogenesis. Therefore, in order to address the uncertainty in regards to the mode of action of acetaldehyde carcinogenesis, and to more accurately determine the risk to health from levels commonly found in Canadian homes taking into account recently published scientific data, this substance was given high priority for a full health risk assessment and development of a Residential Indoor Air Quality Guideline (RIAQG).

The present document reviews the epidemiological, toxicological, and exposure research on acetaldehyde, as well as the conclusions from a number of comprehensive reviews from internationally recognized health and environmental organizations. The document places an emphasis on research published since the most recent comprehensive review, and proposes new short- and long-term indoor air exposure limits. This RIAQG for acetaldehyde is intended to provide recommended exposure limits which would minimize risks to human health and support the development of actions to limit acetaldehyde emissions. This document also shows that, when compared to the newly proposed guidelines, levels in Canadian houses do not present a health risk.

Sources and Exposure

Acetaldehyde is found ubiquitously throughout the ambient environment. Natural outdoor sources include higher plant respiration processes and emissions from forest fires. Combustion represents a major anthropogenic source of acetaldehyde, through incomplete combustion of organic material and fuels in motor vehicles. Emissions from industrial production, storage, transport or disposal of products with residual acetaldehyde can also contribute to ambient concentrations. Secondary formation of acetaldehyde can occur through the oxidation of natural and anthropogenic volatile organic compounds (VOCs) present in the atmosphere.

There are numerous sources of acetaldehyde emissions in the indoor environment, often resulting in higher levels compared to outdoors. Incomplete combustion in fireplaces, wood-burning stoves and environmental tobacco smoke, along with certain cooking processes (notably those which use cooking oil), can emit significant quantities of acetaldehyde indoors. Emissions from products for interior finishes (e.g., vinyl flooring and carpets) and wood-based building materials (e.g., fiberboard and particleboard) as well as paints, stains, adhesives, caulking and foam sealants, may also contribute to indoor levels of acetaldehyde. An additional source of acetaldehyde indoors is from the infiltration of vehicle exhaust fumes into the home from an attached garage.

Some consumer products may directly contribute to indoor acetaldehyde levels, such as fragranced consumer products (e.g., air fresheners, liquid fabric softeners, dryer sheets, which may contain acetaldehyde), as well as indirectly via secondary formation of acetaldehyde from indoor reactions of ozone with other organic aerosols. Elevated indoor acetaldehyde levels have been shown to be associated with higher occupant density, likely due to "occupant activities" including, but not limited to, respiration releasing endogenously produced acetaldehyde.

Median acetaldehyde levels from Health Canada exposure studies measured in four cities (Edmonton, Halifax, Regina and Windsor) during winter and summer from 2005 to 2010 ranged from 10.5 to 48.7 $\mu g/m^3$ (indoors) and from 2.4 to 7.2 $\mu g/m^3$ (outdoors) (Health Canada 2010a, 2010b, 2012, 2013). In one study (Windsor), personal exposure measurements were also collected, with a median range of 18.6 to 39.3 $\mu g/m^3$. In these studies, the ratio of indoor to outdoor acetaldehyde concentrations was in general consistently above 2.5, which is indicative of a predominance of indoor sources of acetaldehyde.

Health Effects

Health effects of exposure to acetaldehyde have been examined in toxicological and controlled human exposure studies, with very little epidemiological evidence related to indoor acetaldehyde exposure. In this assessment, the short-term exposure limit is derived from the results of a controlled human exposure study, whereas the long-term exposure limit is based on toxicological data from a study in a rodent model. Supporting evidence is provided by the results of other toxicological and controlled human exposure studies.

Based on the evidence from human and toxicological studies, the effects of short-term and long-term acetaldehyde inhalation are observed at the site of entry. Key health effects include tissue damage and cancer development, mainly in the upper respiratory tract.

Human studies

From the studies with human participants, acute exposure induced eye irritation and potentiated the bronchoconstriction response to methacholine challenge at acetaldehyde concentrations as low as 22 mg/m^3, with nose and throat irritation reported at 50–200 ppm (89–357 mg/m^3) (Myou et al. 1994b; Silverman, Schulte and First 1946). At higher concentrations (350–1,000 mg/m^3), aerosolized acetaldehyde was shown to directly cause bronchoconstriction in people with asthma (Myou et al. 1993,1994b, 1994c, 1995; Fujimura et al. 1997; Prieto et al. 2000, 2002a, 2002b), and a bronchoconstrictive effect was induced in people with allergic rhinitis (2,240 mg/m^3) (Prieto et al. 2002b). Epidemiological data on the long-term effects in humans are limited to a single cross-sectional study of school children (Flamant-Hulin et al. 2010), demonstrating a significant association between acetaldehyde exposure (measured in classrooms) and increased pulmonary inflammation for non-asthmatic children, but not for asthmatic children.

Toxicological studies

In laboratory animals, acute acetaldehyde exposure induced irritation and bronchoconstriction responses. For sensory irritation, the lowest concentration that elicited a 50% decrease in respiratory rate was 2,845 ppm (5,080 mg/m^3) for a 10–minute exposure in mice (Steinhagen and Barrow 1984), while exposure at ≥ 25 ppm (45 mg/m^3) acetaldehyde in rats increased vasodilation in the upper respiratory tract (Stanek et al. 2001).

In animal studies, long-term inhalation exposure to acetaldehyde caused a number of non-neoplastic effects primarily in the upper respiratory tract, specifically inflammation and tissue injury (degeneration, hyperplasia, and metaplasia). In rat studies, long-term acetaldehyde exposure caused adverse effects in the olfactory and respiratory epithelia of the nasal cavity, with lesions noted at exposure concentrations as low as 268 mg/m^3, and tissue injury sometimes reported in the larynx, pharynx, and trachea, typically at higher exposure levels (Woutersen et al. 1984, 1986; Saldiva et al. 1985; Appelman et al. 1986; Woutersen and Feron 1987; Cassee et al. 1996; Cassee, Groten and Feron 1996; Oyama et al. 2007; Dorman et al. 2008; Feron, Kruysse and Woutersen 1982). In hamster studies, tracheal and laryngeal tissues were more sensitive than the nasal cavity, although effects were observed at higher concentrations than in the rat studies (Kruysse, Feron and Til 1975; Feron 1979; Feron, Kruysse and Woutersen 1982), indicating a species-related difference. In a small number of animal studies, other adverse effects, namely reduced pulmonary bactericidal activity (Aranyi et al. 1986), increased airway hyperresponsiveness (Kawano et al. 2012), neurological effects (Ortiz, Griffiths and Littleton 1974; Shiohara et al. 1985), and altered gonad weight (Kruysse, Feron and Til 1975) were noted. Growth retardation and mortality were observed at the highest exposure levels (4,464–8,929 mg/m^3) (Kruysse, Feron and Til 1975; Feron 1979; Feron, Kruysse and Woutersen 1982).

The International Agency for Research on Cancer (1999) categorized acetaldehyde as a class 2B carcinogen (possibly carcinogenic to humans). Acetaldehyde has been shown to be genotoxic and mutagenic, inducing DNA damage in the form of DNA adducts, DNA–DNA crosslinks, DNA–protein crosslinks as well as more complex adducts (reviewed in Albertini 2013), and mutagenicity in *in vitro* test systems (Environment Canada and Health Canada 2000) as well as in an *in vivo* inhalation study in aldehyde dehydrogenase 2 (ALDH2) knockout mice (Kunugita et al. 2008). Chronic inhalational exposure has caused carcinogenic effects in rats and hamsters at concentrations that induce tissue changes in the upper respiratory tract, with similar species-related differences in concentrations consistent with the non-neoplastic effects. In rats, chronic exposure resulted in a concentration-dependent increase in adenocarcinoma of the olfactory epithelium and squamous cell carcinoma of the respiratory epithelium occurring at the lowest exposure level (1,339 mg/m^3) (Woutersen et al. 1986). In hamsters, chronic exposure at ≥ 2,946 mg/m^3 acetaldehyde resulted in a significant increase in tumour incidence of the larynx (Feron 1979; Feron, Kruysse and Woutersen 1982).

Susceptible sub-populations

Studies of short-term exposures in human volunteers provide evidence for asthmatics being a sensitive subgroup to inhaled acetaldehyde (Myou et al. 1993; Prieto et al. 2000, 2002b). An ALDH2 polymorphism (ALDH2-2, the non-functional variant, prevalent in 40 to 50% of the Asian population, which greatly alters the rate of acetaldehyde metabolism following alcohol consumption) may confer additional susceptibility to acetaldehyde exposure. Although an increased severity of acetaldehyde-induced effects has been demonstrated in studies using ALDH2

knockout mice (as compared to wild-type mice) (Isse et al. 2005; Oyama et al. 2007, 2010), in human studies, no significant difference in hyperresponsiveness was observed following inhaled aerosolized acetaldehyde (Teeguarden et al. 2008).

Mode of Action for Carcinogenesis

The weight of evidence points to a non-linear (or threshold) mode of action (MOA) for acetaldehyde carcinogenesis. The pattern of genotoxicity and mutagenicity is consistent with a cytotoxic (secondary to a proliferative response), rather than mutagenic (critical early event), MOA for carcinogenicity. Tumour development is proposed to be related to the occurrence of tissue damage and is dependent on saturation of capacity for acetaldehyde metabolism, enhanced cellular proliferation, and mutation in the nasal cavity.

There is evidence that the toxic effects of acetaldehyde may be due, in part, to an overwhelming of the acetaldehyde detoxification capacity at the site of exposure. Evidence indicates that acetaldehyde toxicity is associated with decreased ALDH activity, and is most predominant in ALDH knockout mouse models. In addition, decreased upper respiratory tract uptake of acetaldehyde at elevated concentrations appears to be related to ALDH activity. Following saturation of the metabolic capacity for acetaldehyde, the carcinogenicity of acetaldehyde is proposed to be dependent on the induction of cytotoxicity, leading to increased cell turnover from recurrent tissue damage and repair. While no studies examining the association between acetaldehyde inhalation and cell proliferation in the upper respiratory tract were identified, enhanced cell proliferation of the tongue, epiglottis, and forestomach (i.e. tissues related to route of entry) was observed in a rat study following administration in drinking water (Homann et al. 1997). In addition, acetaldehyde has been shown to induce DNA damage in the form of DNA adducts, DNA-DNA crosslinks, DNA-protein crosslinks as well as more complex adducts. These types of damage, under certain conditions including at high exposure concentrations and in association with tissue damage, lead to mutation.

The pattern of key events leading to tumour development resembles that observed for formaldehyde which is also proposed in the literature to act via a non-linear MOA for carcinogenesis. There is a high degree of similarity in formaldehyde and acetaldehyde carcinogenesis, including similarities in the structure and toxicity of the two compounds, the critical key events including DNA–protein crosslink formation, development of nasal carcinomas in animals at highly irritating and damaging concentrations, and limited evidence of genotoxicity *in vivo*.

Residential Indoor Air Quality Guideline for Acetaldehyde

The determination of a RIAQG is carried out in two stages. First, a reference concentration (RfC) is derived by applying uncertainty factors to the concentrations at which the most sensitive adverse health endpoint was observed. The RfC approach is used for the determination of a guideline to reduce potential health impacts such as those observed in key toxicological, controlled human exposure, and indoor epidemiological studies.

For the short-term exposure RfC, the exposure period is specified; in the present case, one hour. For the long-term exposure RfC, the exposure is considered to occur over months or years, up to a lifetime.

In the second stage, the short- and long-term exposure RfCs are compared with measured exposures in residential indoor air, and evaluated with respect to their technical feasibility. If the RfC is considered attainable where reasonable control measures are followed, the RIAQG is set equal to the RfC. If the RfC is considered unattainable with currently available risk management technology and practices, the RIAQG may be set at a higher concentration. Setting the RIAQG at a higher concentration than the RfC results in a smaller margin of exposure between the RIAQG and the concentration at which effects have been observed in health studies. Nonetheless, a RIAQG derived in this manner does provide a measure of health protection, while remaining an achievable target for improving indoor air quality when evaluating risk management measures.

Short-term Residential Indoor Air Quality Guideline

For short-term exposure to acetaldehyde, in a study investigating bronchoconstriction response in human volunteers, a provocative concentration required to produce a 20% fall in forced expiratory volume in one-second (FEV_1) geometric mean for asthmatic subjects of 527 mg/m^3 (95% CI: 142–1,149 mg/m^3) acetaldehyde following a 2-minute exposure was identified (Prieto et al. 2000). The lower 95% confidence level of 142 mg/m^3 was chosen as the point of departure, and uncertainty factors (UFs) of 10 to account for a use of a lowest observed adverse effects level (LOAEL) and 10 to account for additional sensitivity in the human population (e.g., more severe asthmatics, children, ALDH polymorphisms) were applied. Thus, the short-term RfC is 1,420 µg/m^3. The Health Canada residential indoor air exposure studies provide a 24–hour integrated sample of acetaldehyde measurements, which does not represent acute or peak exposure. It is evident from these 24–hour measurements that the short-term reference exposure level is significantly higher than the median range of indoor air concentrations. Therefore, as this exposure limit is achievable in Canadian homes, the proposed short-term RIAQG for acetaldehyde is 1,420 µg/m^3.

It is recommended that the short-term exposure limit be compared to a one-hour air sample.

Long-term Residential Indoor Air Quality Guideline

For chronic exposure, the most sensitive neoplastic endpoint was adenocarcinoma in the nasal cavity of male rats, with the most sensitive non-neoplastic endpoint being degeneration of the olfactory epithelium in rats. As discussed above, a strong body of evidence has also emerged to support the notion that acetaldehyde exerts its carcinogenic effect through a non-linear MOA, with non-neoplastic effects being precursors to a carcinogenic response. Therefore, derivation of an RfC for the neoplastic effects of acetaldehyde is based on the observation of the non-neoplastic effects. A no observed adverse effect level (NOAEL) of 89 mg/m^3 is selected, based on degeneration of the olfactory epithelium in rats (Dorman et al. 2008). Using an upper respiratory tract physiologically-based pharmacokinetic model for acetaldehyde inhalation, the human equivalent concentration (HEC) calculated is 120 mg/m^3. This value is adjusted for continuous exposure, resulting in an adjusted HEC of 21 mg/m^3. Uncertainty factors of 2.5 to account for toxicodynamic differences between animals and humans, 10 for additional sensitivity in the human population, and 3 for uncertainty in the shape of the lower region of the concentration-response curve were

applied, resulting in a total UF of 75. Thus, the long-term RfC is 280 $\mu g/m^3$. The range of median indoor air acetaldehyde concentrations measured in Canadian homes from the Health Canada residential indoor air exposure studies for a 24–hour averaging period was 10.5 to 48.7 $\mu g/m^3$, with the 95th percentile ranging from 35.6 to149.5 $\mu g/m^3$. This indicates that Canadian homes would not exceed the RfC of 280 $\mu g/m^3$. Therefore, the proposed long-term RIAQG for acetaldehyde is 280 $\mu g/m^3$.

When comparing a measured acetaldehyde concentration with the long-term exposure limit, the sampling time should be at least 24 hours.

Residential Maximum Exposure Limits for Acetaldehyde

Exposure period	Concentration $\mu g/m^3$	ppb	Critical Effects
Short-term (1 hour)	1,420	795	Increased airway responsiveness in asthmatics
Long-term (24 hours)	280	157	Olfactory epithelial degeneration in the nasal cavity of rats

Levels of acetaldehyde in a typical Canadian home are likely well below both the short-term and long-term exposure limits, and accordingly are unlikely to pose a health risk.

Strategies for reducing exposure to acetaldehyde include controlling indoor emissions from combustion appliances and smoking. Control measures include the following:

- Not smoking inside the home.
- Properly install and maintain combustion appliances used for heating (e.g., gas and oil furnaces, wood stoves, gas water heaters), with venting outside.
- Use a higher fan setting when cooking on a gas stove, ensure that it vents outside, and preferentially use the back burners.
- When using and applying consumer products such as paints, adhesives, coatings and lubricants, inks, nail polish remover, and fragrances in the home, the area should be well ventilated, and the user should follow all label recommendations. These products should be kept well sealed and/or in non-occupied areas of the home not connected to the ventilation system, where possible.
- Prevent leaks from an attached garage to the house and make sure that there is an appropriate seal between the home and the garage, particularly for any door that connects the two.
- When performing home renovations, including installation of carpeting or vinyl flooring, and painting in the home, the area should be well-ventilated and the user should follow all label recommendations.

Use of these strategies will help reduce exposure to acetaldehyde and other indoor air contaminants, particularly those in combustion gases and consumer products, including other VOCs.

PREAMBLE

Health Canada assesses the health risks posed by specific indoor pollutants in residential environments and provides recommendations on how to reduce those risks. The science assessment document summarizes the known health effects, pollutant sources and exposure levels in Canadian homes, and characterizes the risks to health based on the best scientific data available. Exposure limits for short- and/or long-term exposure to the pollutant may be developed, representing indoor air concentrations below which health effects are unlikely to occur.

The science assessment document also presents the Residential Indoor Air Quality Guideline (RIAQG) for the pollutant. The RIAQG is a recommended exposure limit, which takes into account the reference concentration for this pollutant and the feasibility of achieving such levels through indoor source control. It may be established for short-term exposure, long-term exposure or both. The RIAQG document also includes recommendations for controlling sources or other actions to reduce exposure.

For some pollutants, a numerical exposure limit may not be developed, although the available scientific evidence justifies reducing Canadians' exposure to the pollutant. In this case, a guidance document that focuses on actions to control sources and reduce exposure is developed.

Science assessment documents and associated RIAQGs and/or guidance documents therefore serve as a scientific basis for activities to evaluate and reduce the risk from indoor air pollutants including, but not limited to:

- assessments by public health officials of health risks from indoor air pollutants in residential or similar environments;
- performance standards that may be applied to pollutant-emitting materials, products, and devices, so that their normal use does not lead to air concentrations of pollutants exceeding these guidelines; and
- communication products informing Canadians of actions they can take to reduce their exposure to indoor air pollutants and protect their health.

The RIAQG and Guidance Documents replace a series of exposure limit values for indoor air pollutants in a report entitled *Exposure Guidelines for Residential Indoor Air Quality* (Health Canada 1987). In addition to updates for the substances included in the 1987 report, guidelines or guidance will be developed for other substances that are identified as having the potential to affect human health in the indoor environment.

The focus of this science assessment document is acetaldehyde, which was identified as a priority for the development of a RIAQG. This was because the indoor air concentrations measured in Canadian homes in Health Canada studies were found to approach or exceed the acetaldehyde inhalation concentration attributed to a cancer risk of 1 in 100,000 obtained from a previous Health Canada assessment (Environment Canada and Health Canada 2000; Health Canada 2015).

In addition to relevant literature, the present document draws from a number of comprehensive reviews of the health effects of acetaldehyde, including:

- *Priority Substances List Assessment Report: Acetaldehyde*, published by Environment Canada and Health Canada in 2000 (Environment Canada and Health Canada 2000)
- *Health Assessment Document for Acetaldehyde*, published by the US Environmental Protection Agency in 1987 (cited hereafter as US EPA 1987)
- *Acetaldehyde as a Toxic Air Contaminant Health Assessment*, published by the California Environmental Protection Agency in 1993 (cited hereafter as CalEPA 1993)
- *Acetaldehyde Reference Exposure Levels*, published by the California Environmental Protection Agency in 2008 (cited hereafter as CalEPA 2008)
- *Environmental Health Criteria 167: Acetaldehyde*, published by the World Health Organization in 1995 (cited hereafter as WHO 1995)

Relevant literature was identified through the aforementioned comprehensive reviews and a web-based search through April 2015, with an emphasis on reviews published since the most recent comprehensive review. The original articles of direct relevance to evaluating exposure to acetaldehyde in the indoor environment and its associated health effects were reviewed. The scope of this document is limited to the inhalation of acetaldehyde, and does not consider dietary sources or oral routes of exposure. Key studies underlying the derivation of guideline values are presented, and where appropriate, supporting information is summarized. In addition, information on acetaldehyde concentrations in Canadian homes as well as factors influencing these concentrations was obtained from Health Canada research studies. At the time of publication of this document, some of these data were pending publication in peer-reviewed literature.

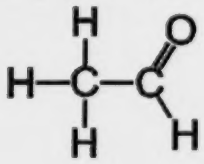
1.0 PHYSICAL AND CHEMICAL CHARACTERISTICS

Acetaldehyde is a colourless, flammable liquid that is volatile at ambient temperature and pressure. It has a pungent and irritating odour that becomes more fruity and pleasant when diluted. Its physical and chemical properties are summarized in Table 1 (WHO 1995; CalEPA 2008).

Table 1. Physical and chemical properties of acetaldehyde

Property	Value
Molecular formula	C_2H_4O
Molecular weight	44.1 g/mol
CAS registry number	75-07-0
Density	0.79 g/cm^3
Vapour pressure	101.3 kPa at 20°C
Water solubility	Miscible in water and most common solvents
Boiling point	20.2°C at 101.3 kPa
Odour threshold	0.09 mg/m^3 (0.05 ppm)
Octanol/water partition coefficient	0.63
Common synonyms	Ethanal, acetic aldehyde, acetylaldehyde, ethylaldehyde, diethylacetal, 1,1-diethyoxy ethane
Conversion factors	1 ppm = 1.7857 mg/m^3 1 mg/m^3 = 0.56 ppm

Chemical structure



2.0 SOURCES IN THE ENVIRONMENT

This section focuses on sources of acetaldehyde in outdoor and indoor air. Additional sources contribute to exposure to acetaldehyde in media other than air, such as food (Environment Canada and Health Canada 2000), but these discussions are beyond the scope of this document.

2.1 Outdoor Sources

Acetaldehyde is found ubiquitously throughout the ambient environment, emitted through both natural and anthropogenic sources (US EPA 2000; Environment Canada 2015).

Natural ambient sources include higher plant respiration processes (US EPA 2000) and forest fires; however, it can be difficult to quantify emissions from these sources, as they are sporadic and often unpredictable (Environment Canada and Health Canada 2000).

Combustion represents a major anthropogenic source of ambient acetaldehyde, through incomplete combustion of organic material (e.g., in woodstoves, fireplaces, as a part of environmental tobacco smoke). Emissions may also result from industrial manufacturing and uses (US EPA 2000) as well as incomplete combustion of fuels in motor vehicles (Environment Canada and Health Canada

2000). In 1994, vehicle combustion exhaust represented the largest direct anthropogenic acetaldehyde source in Canada. From 2004 to 2010, a small decline in ambient acetaldehyde levels was observed (Stroud et al. 2015). Following the previous Environment Canada and Health Canada acetaldehyde assessment (2000), management measures for a variety of pollutants, including acetaldehyde, were put in place under the *Canadian Environmental Protection Act, 1999*.

In industry, acetaldehyde is used to make acetic acid, pyridine, and butylene glycol (NTP 2014). Industrial releases of acetaldehyde can occur from any stage of the production, storage, transport or disposal of products with residual acetaldehyde. Canada's National Pollutant Release Inventory indicated that in 2015, on-site releases from all industrial facilities totalled 2090 tonnes (Environment Canada 2015). Of this, almost 100% (2082 tonnes) was released to air with the remainder to water. Even with few releases of acetaldehyde to water and possibly soil, transfer to air from water and soil is expected due to its high vapour pressure.

Several atmospheric processes exist that contribute to ambient acetaldehyde levels. Secondary formation of acetaldehyde can occur through the oxidation of natural and anthropogenic volatile organic compounds (VOCs) present in the atmosphere. The photochemical oxidation of atmospheric hydrocarbons through free radical/hydroxyl reactions can also cause acetaldehyde formation (Environment Canada and Health Canada 2000). In general, its half-life in the atmosphere, especially in sunny conditions, is less than 10 days, thus limiting the potential for long range transport (Environment Canada and Health Canada 2000). Similarly, irradiation of humic substances in water by sunlight can cause emissions into the atmosphere (Environment Canada and Health Canada 2000).

2.2 Indoor Sources

There are numerous sources of acetaldehyde emissions in the indoor environment, often resulting in higher levels compared to outdoors. Incomplete combustion in fireplaces, wood-burning stoves, and environmental tobacco smoke can emit significant quantities of acetaldehyde indoors (CalEPA 1993; US EPA 2000). In a Health Canada study (2010a), acetaldehyde levels were higher in homes of smokers compared to non-smokers (Table 2). In another study, indoor acetaldehyde levels were also associated with smoking in the home (Brown et al. 2015). Acetaldehyde can also be released from some cooking processes (notably with the use of cooking oil) (Environment Canada and Health Canada 2000). Additionally, the infiltration of vehicle exhaust may increase indoor exposure concentrations (Environment Canada and Health Canada 2000).

Indoor sources of acetaldehyde include interior finish products (e.g., vinyl flooring and carpets) and wood-based building materials (e.g., fiberboard and particleboard) (CalEPA 2008). Acetaldehyde was found to be one of the predominant air pollutants in homes with recent home renovations, such as painting or installation of new carpeting (Hodgson, Beal and McIlvaine 2002). Studies have observed higher concentrations in homes with "wall-to-wall" carpeting compared to hard surface flooring (Dassonville et al. 2009) as well as an association between indoor acetaldehyde concentrations and the quantity of particle board furniture in a home (Hodgson, Beal and McIlvaine 2002). In addition, the year of construction of a home has been found to be a predictor of acetaldehyde concentrations in a Health Canada study conducted in Edmonton and Halifax, with newer homes having higher concentrations (Héroux et al. 2011).

A Canadian database of emissions from commonly used building materials reported 32 of 69 products tested emitted acetaldehyde (Won et al. 2005). The materials were selected to represent building materials commonly used in Canadian homes. Acetaldehyde emissions were detected in solid materials such as oriented strand board, medium-density fibreboard, carpets, laminates, and linoleum/vinyl flooring, but not in plywood, solid wood or underpad. Among the solid consumer products in this study, oriented strand board had the highest emission factor (maximum 265.5 $\mu g/m^2$/hour). Maximal emissions from other solid consumer products were lower: medium-density fibreboard (89.9 $\mu g/m^2$/hour), carpet (20.9 $\mu g/m^2$/hour), laminates (11.49 $\mu g/m^2$/hour), and linoleum/vinyl flooring (28.5 $\mu g/m^2$/hour). Note, however, that while the emission factors provide information on the rate of emissions, direct comparisons may be misleading, as the quantity of the material used in the indoor environment (either by mass or by area) is not accounted for. More recent studies have also reported acetaldehyde emissions from flooring, carpet, medium-density fibreboard, oriented strand board, paints, stains, adhesives, caulking, and foam sealants (Won et al. 2013; Won et al. 2014).

Some consumer products contribute to indoor acetaldehyde levels. It has been demonstrated that acetaldehyde is emitted from fragranced consumer products (e.g., air fresheners, liquid fabric softeners) (Steinemann 2009; Steinemann, MacGregor, et al. 2011). A recent study on the VOC emissions from clothes washers and dryers (using detergents and dryer sheets) detected acetaldehyde in the dryer tests with dryer sheets but not the washing machine experiments (Steinemann 2009; Steinemann, Gallagher, et al. 2011). The dryer sheets did not indicate the presence of acetaldehyde on the product labels, and the authors suggested that it may be formed through secondary reactions (Steinemann, Gallagher, et al. 2011). It is also possible that acetaldehyde was present in the dryer sheets themselves.

Small amounts of acetaldehyde are used in products such as perfumes, deodorizers, polyester resins, basic dyes, preservatives for fruit and fish, flavouring agents, denaturant of alcohol, fuels, gelatin hardeners, and as a solvent in the rubber, tanning, and paper industries (US EPA 2000).

Endogenous acetaldehyde production occurs in the human body during the breakdown of sugars and ethanol (due primarily to alcohol consumption) (Environment Canada and Health Canada 2000; US EPA 2000), which may contribute to acetaldehyde concentrations in the indoor environment.

In a study of 40 Australian homes, elevated indoor acetaldehyde levels were associated with higher occupant density due to what the authors refer to as "occupant activities", which include respiration and cooking (Cheng et al. 2015).

There is some evidence to suggest that indoor reactions of ozone and organic aerosols (e.g., VOCs from household products) can initiate the secondary formation of other pollutants such as acetaldehyde. One study found that acetaldehyde emission levels from some scented household cleaning products increased in the presence of ozone (Destaillats et al. 2006). A chamber study in which carpet samples were tested for VOC emissions in the presence or absence of ozone showed increases in aldehyde emission rates in the presence of ozone, although acetaldehyde increases were minimal (Morrison and Nazaroff 2002). In an additional chamber study, emissions of

acetaldehyde from a kitchen cleaning agent and a plug-in air freshener were increased under high ozone test concentrations (Nørgaard et al. 2014).

3.0 INDOOR AND OUTDOOR CONCENTRATIONS

Canadian indoor and outdoor exposure concentrations of acetaldehyde from Health Canada studies are presented in Table 2. These studies are considered to be the most recent and most representative data available for quantifying long-term levels of exposure in Canadian homes.

Median acetaldehyde levels measured in four cities (Edmonton, Halifax, Regina, and Windsor) during winter and summer from 2005 to 2010 ranged indoors from 10.5 to 48.7 $\mu g/m^3$ and outdoors from 2.4 to 7.2 $\mu g/m^3$. The 95th percentile values ranged indoors from 35.6 to 149.5 $\mu g/m^3$ and outdoors from 7.6 to 17.6 $\mu g/m^3$.

Personal exposure measurements were only collected in the 2005 Windsor study. Acetaldehyde concentrations were found to have a median range of 18.6 to 39.3 $\mu g/m^3$ and a 95th percentile range of 54.7 to 101.7 $\mu g/m^3$ (Health Canada 2010b).

Among other pollutants, the Relationships of Indoor, Outdoor and Personal Air (RIOPA) study reported indoor levels of acetaldehyde for 100 homes in three US cities, namely Elizabeth, New Jersey, Houston, Texas, and Los Angeles County, California (Weisel et al. 2005). The median range of acetaldehyde measured indoors was 13.9 to 24.3 $\mu g/m^3$, which falls within the range of values reported in the Canadian studies. Similar acetaldehyde levels were measured in a study of 490 homes in France, with the median indoor level reported at 11.0 $\mu g/m^3$ (range: 1.8–94.6 $\mu g/m^3$) (Billionnet et al. 2011).

Table 2. Indoor, outdoor, and personal concentrations (µg/m³) of acetaldehyde in Canada

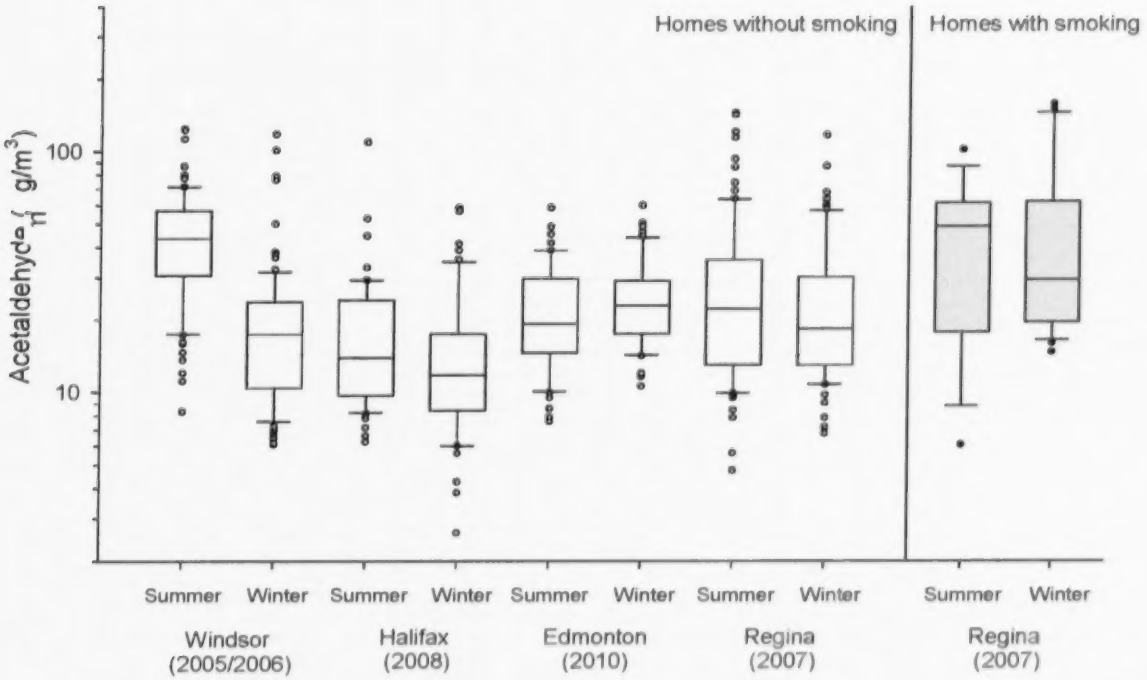
Location	Sampling period	Sampling method[a]	Season	No. of homes	Smoking status	No. of samples[b]	Concentration (µg/m³) Min	Median	95th %ile	Max	Reference
INDOOR											
Edmonton, Alberta	2010	Summa canisters (7 days × 24 hours)	Summer	50	Non-smokers	328	4.5	17.7	54.4	113.5	Health Canada (2013)
			Winter	50		337	3.0	18.8	50.6	188.1	
Halifax, Nova Scotia	2009	Summa canisters (7 days × 24 hours)	Summer	50	Non-smokers	331	1.1	13.1	48.2	681.0	Health Canada (2012)
			Winter	50		312	2.1	10.5	45.7	143.2	
Regina, Saskatchewan	2007	Summa canisters (24 hours)	Summer	111	Non-smokers	91	4.7	22.3	114.3	275.4	Health Canada (2010a)
					Smokers	13	6.1	48.7	101.7	101.7	
			Winter	106	Non-smokers	83	6.8	18.3	60.2	116.9	
					Smokers	21	14.7	29.3	149.5	157.4	
Windsor, Ontario	2006	Summa canisters (5 days × 24 hours)	Summer	46	Non-smokers	211	5.7	40.2	90.7	128.4	Health Canada (2010b)
			Winter	47		224	4.0	12.6	35.6	78.4	
Windsor, Ontario	2005	Summa canisters (5 days × 24 hours)	Summer	45	Non-smokers	217	0.01	45.0	95.7	185.7	Health Canada (2010b)
			Winter	48		232	4.4	16.3	62.9	509.7	
Overall range from all studies							**0.01–14.7**	**10.5–48.7**	**35.6–149.5**	**78.4–681.0**	
OUTDOOR											
Edmonton, Alberta	2010	Summa canisters (7 × 24 hours)	Summer	50	—	324	1.9	7.2	17.6	55.7	Health Canada (2013)
			Winter	50		332	0.9	3.3	9.3	21.7	
Halifax, Nova Scotia	2009	Summa canisters (7 × 24 hours)	Summer	50	—	324	1.2	3.3	8.0	286.6	Health Canada (2012)
			Winter	50		286	0.7	2.5	9.2	41.4	
Regina, Saskatchewan	2007	Summa canisters (24 hours)	Summer	111	—	108	2.3	6.3	15.6	32.1	Health Canada (2010a)
			Winter	106		94	1.3	4.8	18.7	39.2	
Windsor, Ontario	2006	Summa canisters (5 × 24 hours)	Summer	46	—	214	2.1	5.9	13.2	39.5	Health Canada (2010b)
			Winter	47		215	1.0	2.4	7.6	20.3	
Windsor, Ontario	2005	Summa canisters (5 × 24 hours)	Summer	45	—	216	2.6	6.2	16.4	38.6	Health Canada (2010b)
			Winter	48		200	1.5	3.2	9.1	15.7	
Overall Range from All Studies							**0.7–2.6**	**2.4–7.2**	**7.6–17.6**	**15.7–286.6**	
PERSONAL											
Windsor, Ontario	2005	Summa canisters (5 × 24 hours)	Summer	45	—	206	10.3	39.3	101.7	151.1	Health Canada (2010b)
			Winter	48		225	8.5	18.6	54.7	104.8	

[a] Stainless steel evacuated Summa™ canisters (6.0 L) were used to non-selectively collect indoor and outdoor air samples over 24-hour periods, in both seasons, for analysis of constituent VOC concentrations. Detailed methodologies for air sampling and analysis can be found in the individual reports.

[b] The number of samples represents the total number of samples collected and analyzed.

The distribution of indoor acetaldehyde concentrations in studies conducted by Health Canada is presented in Figure 1. It should be noted that for the studies in Edmonton, Halifax, and Windsor, multiple measurements were made at each home, and these values were averaged to present one value per home, while for the Regina study a single measurement was made at each home.

Figure 1. Distribution of indoor acetaldehyde concentrations by season across studies conducted by Health Canada

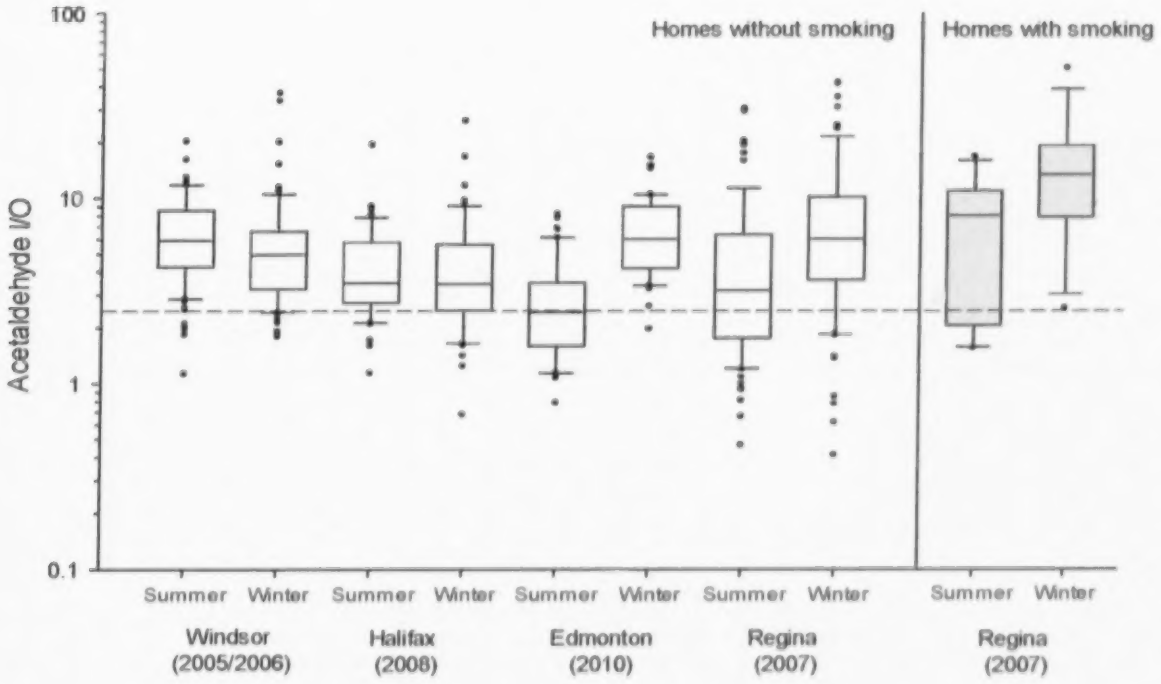


Source data: Health Canada (2010a, 2010b, 2012, 2013)

The 75th, 50th, and 25th percentiles are represented by the top, middle, and bottom of the boxes. The whiskers represent the 90th and 10th percentiles. Outliers are represented by open circles.

The distribution of indoor/outdoor (I/O) ratios for each home is presented in Figure 2. An I/O ratio compares levels of acetaldehyde measured inside a given home to levels measured directly outside the same home. In these studies, the I/O ratios much greater than 2.5 were generally consistent across cities and seasons and are indicative of a predominance of indoor sources of acetaldehyde. I/O ratios were lower in the summer seasons in Regina and Edmonton, suggesting an increased infiltration of outdoor air.

Figure 2. Distribution of I/O ratios by season across studies conducted by Health Canada



Source data: Health Canada (2010a, 2010b, 2012, 2013)

The 75th, 50th, and 25th percentiles are represented by the top, middle, and bottom of the boxes. The whiskers represent the 90th and 10th percentiles. Outliers are represented by open circles. Dotted line represents an I/O of 2.5.

Acetaldehyde levels indoors are increased with decreased ventilation. Increased indoor relative humidity and CO_2, a surrogate measure of ventilation, were positively correlated with increased acetaldehyde, although increased acetaldehyde levels were not associated with increased temperature. Dassonville et al. (2009) observed that the two factors negatively associated with indoor concentrations were (1) the presence of mechanical ventilation, and (2) the amount of time windows were open (temperature was not independently correlated with indoor concentrations).

Along with the association with decreased ventilation, increased acetaldehyde levels were strongly associated with decreased ventilation rate, along with cooking oil usage and the smoking of cigarettes (winter models only) in homes measured in Regina (Héroux et al. 2010). In other studies, decreased acetaldehyde levels were associated with increased ventilation (measured as air exchange rate) and increased absolute humidity (Brown et al. 2015). More specifically, in a study conducted in 50 homes in Edmonton and Halifax, an increase by one in the air exchange per hour was associated with a 57% and 40% decreased change in acetaldehyde levels for these two cities, respectively (Héroux et al. 2011).

4.0 TOXICOKINETICS

4.1 Absorption, Distribution, Metabolism, and Excretion

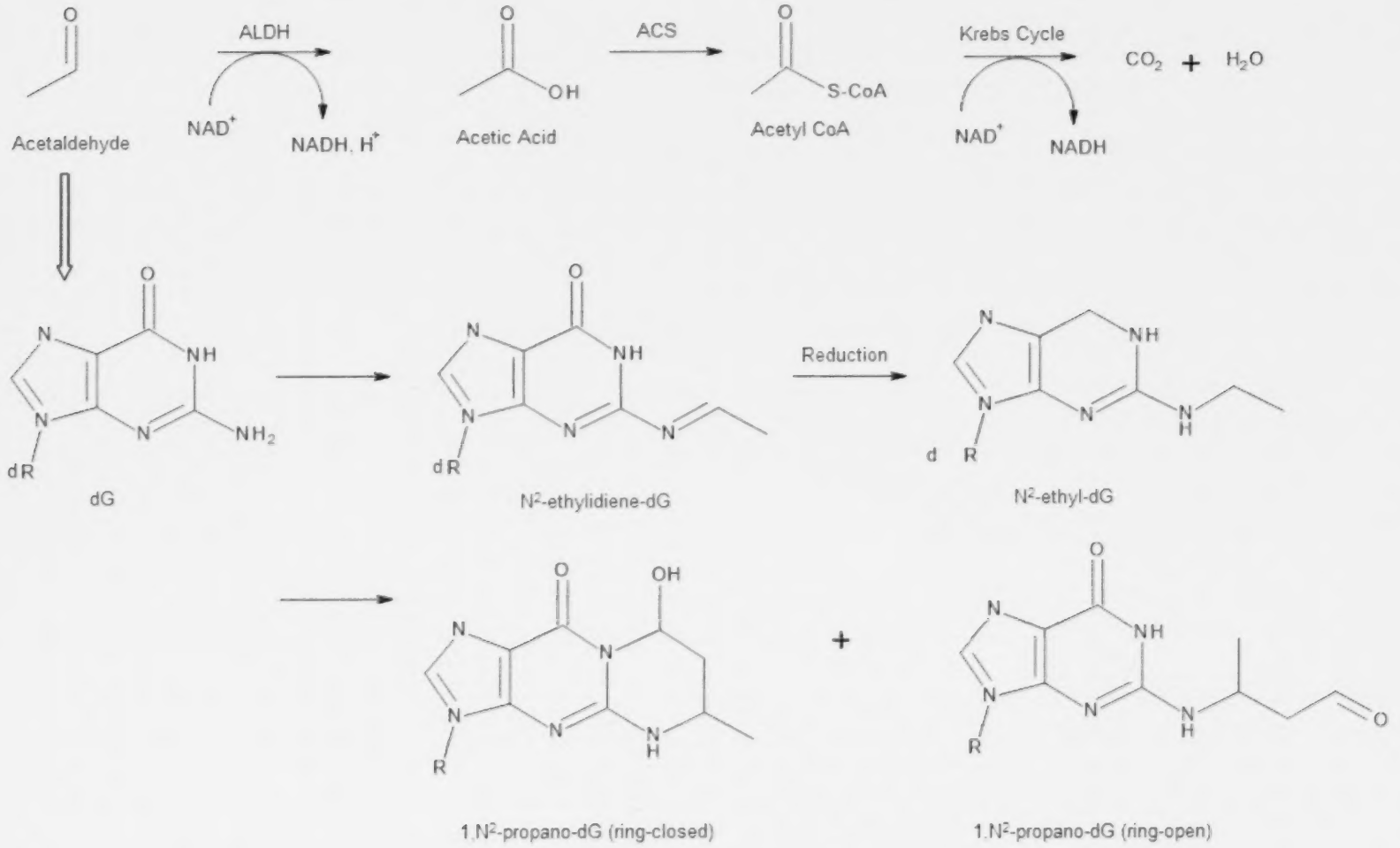
Following inhalation exposure, the majority of acetaldehyde is retained at the site of contact, where it rapidly and irreversibly binds to free protein and non-protein sulfhydryl groups, including cysteine and glutathione (Environment Canada and Health Canada 2000). In human volunteers (n = 8) exposed to acetaldehyde vapour (average concentration of 0.4 to 0.6 µg/L), retention of acetaldehyde ranged from 45 to 70% based on acetaldehyde levels in expired air (Egle Jr. 1970). In this study, retention was primarily dependent on the duration of the ventilatory cycle (i.e., contact time in the respiratory tract) and was not different for inhalation by nose or mouth. Similar levels of retention were observed in a study with dogs, and greater retention was found in the upper versus lower respiratory tract (Egle Jr. 1972). Deposition efficiency of acetaldehyde in the upper respiratory tract of F344 rats was reduced with increasing exposure concentration (Morris and Blanchard 1992). The authors suggested this was related to the overwhelming of the nasal metabolic capacity for acetaldehyde.

While most acetaldehyde remains at the site of contact following inhalation exposure, some studies have detected measurable levels in tissues, indicative of systemic distribution. In animal studies, acetaldehyde was detected in blood, liver, kidneys, spleen, heart muscle, and skeletal muscle of Sprague-Dawley rats exposed to acetaldehyde vapour (1 to 20 mM) for 1 hour (Hobara et al. 1985). The concentration of acetaldehyde was highest in blood immediately following the exposure period, and aortic blood levels were 55% greater than in the peripheral venous blood. Levels in kidney, spleen, heart muscle, and skeletal muscle were less than in blood, and levels in the liver were the lowest. Similarly, following inhalation of acetaldehyde vapour (9 mg/L to 1 g/L for one hour) in Sprague-Dawley rats, levels in blood were greater than in liver (Watanabe, Hobara and Nagashima 1986). These observations suggest that the majority of inhaled acetaldehyde was metabolized in peripheral tissues including lungs, while only a minority reaches the liver where it is rapidly metabolized.

The principal pathway for metabolism of acetaldehyde is by aldehyde dehydrogenase (ALDH), for which there are two isoforms, ALDH1 and ALDH2. ALDH oxidizes acetaldehyde to acetic acid, which is subsequently converted to acetyl-CoA by acetyl-CoA synthetase (ACS) (WHO 1995). Acetyl-CoA enters the Krebs cycle and is further metabolised to CO_2 and H_2O. Acetaldehyde metabolism is NAD^+-dependent, producing protons (H^+) as a by-product. Under certain conditions

(e.g., high exposure concentrations), this can result in tissue acidification (Bogdanffy et al. 2001). Figure 3A summarizes the main pathway for acetaldehyde metabolism. ALDH is found in most mammalian tissues with the highest activities in the liver. Isozymes of ALDH have been identified in respiratory and nasal tissues of rats (Casanova-Schmitz, David and Heck 1984; Bogdanffy, Randall and Morgan 1986). In humans, polymorphisms in the genes encoding ALDH isozymes alter the rate of acetaldehyde oxidation. A polymorphism of the ALDH2 gene, referred to as ALDH2-2, is found in approximately 40 to 50% of the East Asian population, and is associated with a loss of ALDH2 activity in mitochondria leading to "flushing" due to accumulation of acetaldehyde following alcohol consumption (WHO 1995; Agarwal 2001). Furthermore, acetaldehyde can interact with DNA-forming adducts, the major reaction occurring on the exocyclic amino group of guanine (Figure 3B) (discussed further in Section 5.4).

Figure 3. Metabolism and genotoxicity of acetaldehyde in the upper respiratory tract
A) Metabolism of acetaldehyde by ALDH and ACS
B) Production of deoxyguanosine DNA adducts, N^2-ethyl-dG and 1,N^2-propano-dG



There is evidence to support that the saturation of the ALDH metabolism pathway occurs with increasing acetaldehyde concentrations. Stanek and Morris (1999) observed a significant, concentration-dependent decrease in acetaldehyde uptake ($p < 0.05$) following inhalation exposure, with the average uptake of acetaldehyde reported as 54, 37, and 34% for 10, 300, and 1,500 ppm (18, 536, and 2,678 mg/m^3), respectively. This concentration-dependent change in uptake was not observed in animals pre-treated with cyanamide, an ALDH inhibitor. Similar results were reported by Morris (1997), who observed decreases in acetaldehyde uptake at high versus low exposure concentrations in mice, rats, hamsters, and guinea pigs. In that study, *in vitro* ALDH activity was also measured for each species; at high concentrations (1,000 ppm, and possibly 100 ppm [1,786 and 179 mg/m^3]), uptake of acetaldehyde exceeded metabolic capacity (i.e., ALDH activity), suggestive of saturation of acetaldehyde metabolic capacity at these concentrations. Together, these studies imply that the metabolism of acetaldehyde is concentration-dependent and reduced at high concentrations (> 300 ppm; 536 mg/m^3) due to saturation of the ALDH metabolic pathway. The authors propose that at high acetaldehyde concentrations (1,500 ppm), uptake may be dominated by removal via the blood stream and/or by direct chemical reaction with tissue substrates (specifically sulfhydryl and amino groups) (Stanek and Morris 1999).

Inhalation studies in rodents have demonstrated rapid, first-order elimination kinetics of acetaldehyde from blood via metabolism, even after exposure to high concentrations (US EPA 1987). Rapid elimination following inhalation was reported by Shiohara et al. (1984) with a half-life of 10 minutes, and 40 minutes to total clearance from blood in rats. Acetaldehyde can also be excreted unchanged in urine and expired air (CalEPA 1993).

Acetaldehyde is also endogenously produced in the body (Section 2.2), including the oral cavity, with a major source being the metabolism of consumed alcohol, which can contribute to total body burden of the chemical (Lachenmeier and Monakhova 2011; Linderborg, Salaspuro and Vakevainen 2011). Exhaled acetaldehyde has been measured in the range of 0.009 to 0.026 mg/m^3 in human subjects that have not been exogenously exposed, and have not consumed alcohol. Higher exhaled acetaldehyde levels were observed in smokers and abstinent alcoholics, as well as in individuals with the ALDH2-2 polymorphism who consumed alcohol (Jones 1995).

4.2 Physiologically based pharmacokinetic modelling

Teeguarden et al. (2008) developed an upper respiratory tract physiologically based pharmacokinetic (PBPK) model for acetaldehyde based on a model constructed for vinyl acetate inhalation (Plowchalk, Andersen and Bogdanffy 1997). The airway model consists of the nasal cavity, nasopharynx, and larynx. For acetaldehyde, the nasal cavity is the primary focus of the model as it is the site of entry of inhaled compounds and location of acetaldehyde-induced lesions.

For the rat, the nasal cavity consists of five regions: dorsal respiratory; anterior and posterior dorsal olfactory; and anterior and posterior ventral respiratory. In humans, the anterior and posterior dorsal olfactory regions are combined due to the smaller size of this tissue. The respiratory tissues are divided into a three-layer substructure: lumen, epithelial cell layer, and submucosal tissue layer. The lumen forms the surface exposed to inhaled air. The epithelial cell layer forms the target site for acetaldehyde toxicity and has metabolic capacity for acetaldehyde clearance. The submucosal tissue layer also has metabolic capacity and is perfused by blood, which clears acetaldehyde and metabolites from the tissue. Acetaldehyde concentrations in the

respiratory and olfactory epithelial tissue were largely a linear function of exposure in both species.

The model includes metabolism of acetaldehyde by ALDH1 and ALDH2, and of acetic acid by ACS. The polymorphisms of ALDH2, which cause reduced enzyme activity, are incorporated into the human component of the model. Evaluation of the model found minimal impact of the non-functional ALDH2-2 polymorphism on the acetaldehyde concentrations in the respiratory and olfactory epithelium. Based on the model results, the authors concluded the majority of the metabolic clearance of acetaldehyde is catalyzed by ALDH1 in nasal tissue

Equations describing the exposure–dose relationship were developed for both rats and humans to replace the PBPK model. These equations empirically related exposure concentration to tissue dose at steady state. By combining the rat and human equations, the human equivalent concentration (HEC) can be determined from the exposure in rats as follows:

$$HEC_{\mu M} = (8.41 \times ppm_{rat} - 7.2)/6.2.$$

5.0 HEALTH EFFECTS

This section provides a review of the effects of acetaldehyde in humans (Section 5.1) as well as relevant toxicological studies in experimental animals, with supporting information from *in vitro* test systems (Section 5.2). A concise summary of the health effects of inhalation exposure to acetaldehyde is presented in Section 5.3, followed by evidence to support a probable carcinogenic mode of action (Section 5.4). Details of the human exposure and toxicological studies presented below can also be found in appendices A and B.

Relevant studies on the health effects of inhaled acetaldehyde published up to April 2015 were reviewed. Although acetaldehyde is a component of tobacco smoke, studies of tobacco smoke were excluded as tobacco smoke is a complex mixture that contains many known toxins and carcinogens, and its health effects are not addressed in this document. Other routes of exposure (i.e., ingestion and dermal) were not considered physiologically relevant. Health Canada evaluated the original studies identified as key in the derivation of this RIAQG for acetaldehyde (Section 6). Other relevant information was drawn from previous authoritative reviews of the health effects of acetaldehyde: (a) the Government of Canada's *Priority Substances List Assessment Report: Acetaldehyde* (Environment Canada and Health Canada 2000); (b) the U.S. EPA's *Health Assessment Document for Acetaldehyde* (US EPA 1987); (c) the California EPA's *Acetaldehyde as a Toxic Air Contaminant Health Assessment* (CalEPA 1993) and *Acetaldehyde Reference Exposure Levels* (CalEPA 2008); and (d) the World Health Organization's *Environmental Health Criteria 167: Acetaldehyde* (WHO 1995).

5.1 Effects in Humans

5.1.1 Respiratory effects

5.1.1.1 Short-term exposure

In a study designed to determine occupational limits, male and female volunteers (n = 12/sex) were exposed to various solvents for 15 minutes. Unspecified irritation was reported at 25 ppm (45 mg/m^3) acetaldehyde, with eye irritation reported at 50 ppm (89 mg/m^3) and nose and throat irritation at 200 ppm (357 mg/m^3) (Silverman, Schulte and First 1946). In another group of 14 healthy adult males, exposure to 134 ppm (239 mg/m^3) acetaldehyde for 30 minutes resulted in mild irritation of the upper airway (Sim and Pattle 1957). In a more recent study, Muttray et al. (2009) evaluated airway irritation in healthy volunteers (n = 20 male adults) exposed to 50 ppm (89 mg/m^3) acetaldehyde in a chamber for four hours. Acetaldehyde exposure did not result in any symptoms of irritation, did not affect olfactory threshold, nor did it significantly alter any markers of inflammation in the upper airways.

Several studies have demonstrated that short-term exposure to acetaldehyde increased the bronchoconstriction response in human volunteers with asthma (Myou et al. 1993; Myou et al. 1994a, 1994b, 1995; Fujimura et al. 1997; Fujimura et al. 1999; Prieto et al. 2002b). In these studies (summarized in Table A2 of Appendix A), subjects inhaled aerosolized acetaldehyde for short periods of time (2–4 minutes), which was followed by pulmonary function and bronchoconstriction provocation tests. The evaluation was repeated with increasing acetaldehyde exposure until forced expiratory flow volume in one second (FEV_1) was reduced by 20% (PC_{20}) or until the highest exposure was reached.

Prieto et al. (2000) evaluated bronchoconstriction in healthy (n = 8 male and 12 female) and mildly asthmatic (n = 24 male and 37 female) Caucasian subjects. Subjects inhaled aerosolized acetaldehyde (5–40 mg/mL; corresponding to150–1,200 mg/m^3) for two minutes. In the asthmatic group, acetaldehyde induced bronchoconstriction in 56 subjects, with a geometric mean PC_{20} of 17.55 mg/mL. Based on the nebulizer operation parameters, this corresponded to an acetaldehyde inhalation exposure of 527 mg/m^3. A high degree of interindividual variation was noted in the participants, with PC_{20} values ranging from 1.96 to 40 mg/mL (59 to 1,200 mg/m^3). Subjects also reported cough, chest tightness, and pharyngeal irritation following acetaldehyde inhalation. No bronchoconstriction was observed in healthy subjects.

In a subsequent study, Prieto et al. (2002b) reported airway responsiveness to inhaled acetaldehyde (0.5–80 mg/mL) in 16 asthmatic subjects (8 males and 8 females) [geometric mean PC_{20} = 35.5 mg/mL (range 8.4 to 80 mg/mL); corresponding to 1,136 mg/m^3], with a milder response in 43 subjects (26 males and 17 females) with allergic rhinitis [geometric mean PC_{20} = 67.6 mg/mL (range 15.5 to 80 mg/mL); corresponding to 2,166 mg/m^3]. No response was observed in a group of 19 healthy subjects (8 males and 11 females). A similar geometric mean PC_{20} of 38.9 mg/mL (corresponding to 1,245 mg/m^3) was observed in a group of 6 male and 10 female mildly asthmatic subjects exposed to acetaldehyde (Prieto et al. 2002a). Subjects also reported cough, difficulty breathing, and throat irritation. In these subsequent studies, the greater PC_{20} values were likely due to evaluation of higher acetaldehyde concentrations (80 mg/mL vs. 40 mg/mL), as subjects that did not have the necessary 20% reduction in FEV_1 were assigned the highest tested concentration as

their PC_{20}. Similar studies by Myou et al.(1993, 1994a, 1994b, 1995) and Fujimura et al. (1999) were conducted with Japanese participants. Due to the ALDH2 polymorphism prevalent in East Asian populations, bronchoconstriction can be observed in individuals following consumption of an alcoholic beverage, a condition described as alcohol sensitivity (Section 4.1). Fujimura et al. (1999) reported a geometric mean PC_{20} of 21.0 mg/mL (corresponding to 588 mg/m^3) in 10 alcohol-sensitive asthmatic subjects exposed to 0.04 to 80 mg/mL (1.12 to 2,240 mg/m^3) acetaldehyde. Additionally, a group of 16 alcohol-insensitive asthmatic subjects had a geometric mean PC_{20} of 31.7 mg/mL (corresponding to 888 mg/m^3) acetaldehyde. Although the PC_{20} was greater in the alcohol-insensitive group as compared to the alcohol-sensitive group, the difference in PC_{20} was not found to be significant.

Myou et al. (1993, 1994a, 1994b 1995) and Fujimura et al. (1997) reported PC_{20} values ranging from 364 to 652 mg/m^3 acetaldehyde, consistent with those from a subsequent study by Fujimura et al. (1999). Of note, these PC_{20} values were concentrations of inhaled acetaldehyde delivered by nebulizer, and then converted to approximate air concentrations. Uncertainty in these conversions results from the model of nebulizer used in these Japanese studies, which is considered to have inconsistent aerosol output and dose delivery (Hollie et al. 1991). Acetaldehyde-induced bronchoconstriction was not observed when asthmatic subjects (n = 9; gender not indicated) were pre-treated with a histamine receptor antagonist, suggesting the effect was associated with histamine release (Myou et al. 1993). Additional studies have demonstrated that selected inhibitors of the cyclooxygenase pathway diminish the bronchoconstrictive effect of inhaled acetaldehyde, thus implicating cyclooxygenase pathway products in acetaldehyde-induced bronchoconstriction (Myou et al. 1994b; Fujimura et al., 1997). Acetaldehyde inhalation (0.8 mg/mL × 4 minutes; corresponding to 22 mg/m^3) potentiated the hyperresponsiveness to methacholine challenge (Myou et al. 1994a), which was also not prevented by pre-treatment with histamine receptor antagonist.

5.1.1.2 Long-term exposure

In a French cross-sectional study of 104 school children (24 male and 46 female non-asthmatics; 20 male and 14 female asthmatics), the relationship between exposure to air pollution and fractional exhaled nitric oxide (FeNO; a marker of airway inflammation) was investigated (Flamant-Hulin et al. 2010). The levels of several air pollutants (i.e., $PM_{2.5}$, nitrogen dioxide, acetaldehyde, and formaldehyde) were measured over a five-weekday period in classrooms and schoolyards. Acetaldehyde concentrations were greater in classrooms than schoolyards, and exposures were grouped as high or low using the third quartile as the cut-off. The mean acetaldehyde levels in classrooms were 9.3 and 16.4 μg/m^3 for low and high exposure groups, respectively. In terms of classroom acetaldehyde exposure, a significant increase in FeNO was noted in non-asthmatic children of the high exposure group compared to the low exposure group; effects were non-significant in the asthmatic children. This increase in log(FeNO) between high versus low exposure groups was 0.16 (95% CI: 0.07–0.26) for non-asthmatic children, and 0.04 (95% CI: -0.07–0.14) for asthmatic children. For non-asthmatic children, the difference corresponded to a 45% increase in FeNO. The association was stronger in non-asthmatic children that were atopic compared to non-atopic ($p = 0.0081$), indicating atopic children were more sensitive. The main limitations of this study was lack of inclusion of co-pollutants and weather conditions in the statistical analysis, the single assessment of FeNO, and lack of accounting for acetaldehyde exposures at home. Children taking corticosteroids were not included in the analysis. Elevated $PM_{2.5}$ and formaldehyde were also associated with an increase in FeNO.

Other studies of long-term acetaldehyde exposure in humans were not identified in the literature.

5.1.2 Reproductive and developmental effects

Reports of reproductive and development effects in humans following acetaldehyde inhalation exposure were not identified in the literature.

As acetaldehyde is a metabolite of ethanol metabolism, it has been suggested that acetaldehyde derived from alcohol consumption may have a role in fetal alcohol syndrome (Langevin et al 2011); however, studies have not established the role of inhaled acetaldehyde in this syndrome.

5.1.3 Carcinogenicity

The International Agency for Research on Cancer (IARC) has classified acetaldehyde as a Group 2B carcinogen (i.e., possibly carcinogenic to humans), as a result of sufficient evidence of carcinogenicity in animals (based on the development of adenocarcinomas and squamous cell carcinomas of the nasal mucosa of rats, and laryngeal carcinomas in hamsters, following inhalation exposure) and inadequate evidence in human studies (IARC 1999). In a separate monograph, IARC also determined that there was sufficient evidence in humans for the carcinogenicity of acetaldehyde associated with the consumption of alcoholic beverages (i.e., Group 1) (IARC 2012). This latter monograph did not address carcinogenicity associated with acetaldehyde inhalation. The role of metabolically-derived acetaldehyde in alcohol-induced carcinogenesis is strongly supported by epidemiological evidence demonstrating that humans with genetic polymorphisms leading to deficiency in oxidation of acetaldehyde have a substantially increased risk for development of alcohol-related cancers. These cancers are typically located in the oesophagus, oral cavity, pharynx, and larynx. Studies of acetaldehyde metabolism following oral ethanol exposure provide support for the carcinogenic potential of acetaldehyde exposure in humans; however, due to differences in route and nature of exposure, alcohol-induced carcinogenesis was not considered to be an appropriate mechanism for quantification of an RIAQG.

Regarding inhalation exposure in humans, IARC (IARC 1999) identified a case series study of workers in chemical plants in the former German Democratic Republic. Nine cancer cases (five bronchial tumours and two carcinomas of the oral cavity) were noted in workers exposed to a mixture of aldehydes, which was higher than the expected frequency of these tumours (Bittersohl 1974; Bittersohl 1975). IARC also noted that all of the cancer cases were smokers, the study employed a small sample size, the exposure was to a mixture of compounds, and the exposed population was poorly defined.

Additional studies of the carcinogenic effects of inhaled acetaldehyde in humans were not identified in the literature.

5.2 Toxicological Studies

5.2.1 Respiratory effects

5.2.1.1 Acute exposure

In an acute inhalation study, Stanek et al. (2001) reported a vasodilatory response in the upper respiratory tract of anesthetized male F344 rats (n = 3–6) exposed to ≥ 25 ppm (45 mg/m^3) acetaldehyde. Vasodilation was noted within three minutes of acetaldehyde exposure. Pre-treatment of the animals with the sensory nerve toxin capsaicin diminished the response, indicating the vasodilatory response was likely mediated through sensory nerves. The authors noted that vasodilation is a common response to irritant gases and may reflect a protective response to remove irritants from the nasal mucosa.

5.2.1.2 Short-term or single exposure

Inhalation of high concentrations of acetaldehyde (1,339–30,002 mg/m^3), for 30 minutes to 4 hours in laboratory animals, resulted in reduced respiratory rate, difficulty breathing, restlessness, and death (CalEPA 2008). The acetaldehyde concentration required to reduce the breathing rate by 50% (RD_{50}; a measure of sensory irritation), based on head- or nose-only exposures for 10–30 minutes, was calculated to be 2,932 ppm (5,236 mg/m^3) for B6C3F1 mice, 2,845 ppm (5,080 mg/m^3) for Swiss-Webster mice, 3,046 ppm (5,439 mg/m^3) for Wistar rats, and 2,991 ppm (5,341 mg/m^3) for F344 rats (Steinhagen and Barrow 1984; Babiuk, Steinhagen and Barrow 1985; Cassee et al. 1996). Increased severity of acute toxicity symptoms, including straggling gait, lachrymation, abnormal deep respiration, and dyspnea, were observed in ALDH2 knockout ($ALDH2^{-/-}$) mice compared to wild-type mice (n = 5/strain) exposed to 5,000 ppm (8,929 mg/m^3) acetaldehyde for four hours (Isse et al. 2005). The $ALDH2^{-/-}$ mice also had elevated blood acetaldehyde levels at the end of the exposure period, reflecting the reduced metabolic capacity.

A concentration-dependent increase in bronchoconstriction was observed in guinea pigs (n = 6) following inhalation of aerosolized acetaldehyde (1.4–11.0 mg/mL) for 15 to 20 seconds (Myou et al., 1994a; Myou et al. 2001). Pre-treatment with an antihistamine prevented the effect, suggesting it is mediated by histamine release (Myou et al. 1994a). In comparison, use of neuropeptide inhibitors had no effect, indicating that tachykinins were not involved in the acetaldehyde-induced bronchoconstriction (Myou et al. 2001).

Studies with allergen-sensitized BALB/c mice (a mouse model of asthma) have reported that intranasal acetaldehyde increased airway resistance and inflammation, while no effects were observed in non-sensitized mice (Matsuse et al. 2007; Kawano et al. 2012).

5.2.1.3 Long-term or repeat exposure

Subchronic and chronic exposures to acetaldehyde vapour have been demonstrated to cause injury to nasal tissue, especially the olfactory mucosa, in laboratory animals.

Exposure to acetaldehyde for 3 to 14 days resulted in histological changes in the respiratory tract in both rats and mice. Cassee, Groten and Feron (1996) reported a greater extent of necrosis in the olfactory epithelium of Wistar rats (n = 5/group) exposed to 1,500 ppm (2,679 mg/m^3) acetaldehyde for 6 hours/day × 3 days compared to rats exposed to 750 ppm (1,339 mg/m^3). More severe lesions were noted in the nasal cavity, larynx, pharynx, and trachea of $ALDH2^{-/-}$ mice compared to wild-type mice (n = 4–5/group) exposed to 500 ppm (893 mg/m^3) acetaldehyde

24 hour/day × 14 days (Oyama et al. 2007). Less severe and fewer lesions were noted in both strains of mice at the 125 ppm (223 mg/m^3) acetaldehyde exposure level.

Appelman, Woutersen and Feron (1982) exposed male and female Wistar rats (n = 10/sex/group) to 0, 400, 1,000, 2,200 or 5,000 ppm (0, 714, 1,786, 3,929, or 8,929 mg/m^3) acetaldehyde for 6 hours/day × 5 days/week × 4 weeks. Lesions were noted in the olfactory epithelium at all concentrations of acetaldehyde (lowest observed adverse effects level [LOAEL] = 714 mg/m^3), with increasing severity at the higher concentrations. Respiratory epithelium effects were noted at 1,786 mg/m^3 and above, and lesions of the laryngeal and tracheal regions were observed at 3,929 and 8,929 mg/m^3. In a follow-up study using 150 and 500 ppm (268 and 893 mg/m^3) acetaldehyde (n = 10 male rats/group), Appelman et al. (1986) reported degeneration of the olfactory epithelium only at 893 mg/m^3, similar to the effects observed at 714 mg/m^3 in the previous study (no observed adverse effect level [NOAEL] of 268 mg/m^3).

Saldiva et al. (1985) reported an intense inflammatory response in the nasal cavities, including hyperplasia of the olfactory epithelium and polymorphonuclear and mononuclear infiltration of the submucosa, of male Wistar rats (n = 12/group) exposed to 243 ppm (434 mg/m^3) acetaldehyde for 8 hours/day × 5 days/week × 5 weeks. Changes in pulmonary mechanics, including increased respiratory frequency, residual volume, total lung capacity, and functional residual capacity, were detected. The absence of alterations to the forced expiratory flow measurements indicated that mechanical damage to the bronchioles may have occurred during the pulmonary function testing. This is further supported by the absence of histopathological effects in areas of the respiratory tract other than the nasal cavity (as described above).

In another study, male F344 rats (n = 12/group/time point) were exposed to 0, 50, 150, 500 or 1,500 ppm (0, 89, 268, 893 or 2,679 mg/m^3) acetaldehyde for 6 hours/day × 5 days/week for 4, 9, 14, 30 or 65 exposure days (13 weeks) (Dorman et al. 2008). Loss of olfactory neurons was observed at ≥ 268 mg/m^3, at each time point examined (≥ 4 days). The severity and extent of the lesions increased with exposure concentration and duration of exposure. No adverse effects were noted in the olfactory epithelium of animals exposed at 89 mg/m^3. At 268, 893, and 2,679 mg/m^3, all animals exhibited degeneration of the olfactory epithelium. Alterations to the respiratory epithelium, including inflammation, hyperplasia, and squamous metaplasia, were observed at ≥ 893 mg/m^3, at each time point examined.

The effects of chronic inhalation of acetaldehyde in rats were described in a series of reports by Woutersen et al. (Woutersen et al. 1984; Woutersen et al. 1986; Woutersen and Feron 1987). Male and female Wistar rats (n = 105/sex/group) were exposed to 0, 750, 1,500 or 3,000/1,000 ppm (0, 1,339, 2,679 or 5,357/1,786 mg/m^3) acetaldehyde for 6 hours/day × 5 days/week for up to 28 months. Due to growth retardation, respiratory distress, weight loss, and mortality in the highest exposure group, the highest exposure concentration was gradually lowered from 5,357 to 1,786 mg/m^3 over 15 months. Growth retardation was noted in male rats at each exposure group and in females at 2,679 mg/m^3 and 5,357/1,786 mg/m^3. Alterations of the nasal olfactory epithelium, including degeneration, hyperplasia, and metaplasia, were noted at each of the exposure levels; a NOAEL was not determined. Histological alteration in the respiratory epithelium and larynx were noted at 2,679 and 5,357/1,786 mg/m^3, and rhinitis and sinusitis were observed at the highest exposure. Separate groups of rats were allowed a 24- or 52-week recovery period following a 52-

week exposure. Some regeneration of the olfactory epithelium was noted in the 1,339 and 2,679 mg/m^3 exposure groups, but not at the highest exposure level.

Studies with hamsters subchronically and chronically exposed to acetaldehyde have reported histological alterations in nasal, tracheal, and laryngeal tissues (Kruysse, Feron and Til 1975; Feron 1979; Feron, Kruysse and Woutersen 1982). In the study conducted by Kruysse et al. (1975), Syrian hamsters (n = 10/sex/group) were exposed to 0, 390, 1,340 or 4,560 ppm (0, 696, 2,393 or 8,143 mg/m^3) acetaldehyde for 6 hours/day × 5 days/week × 90 days. At the high exposure level, growth retardation, ocular and nasal irritation, and histological changes in the respiratory tract were observed, along with tissue effects including necrosis, inflammation, hyperplasia and metaplasia in the nasal cavity, larynx, trachea, bronchi, and lungs. The severity of effects was greater in the upper respiratory tissues. At the mid-exposure level, mild lesions were observed in the trachea. While increased kidney weights were observed in male, not female, hamsters, no other sex-related differences in adverse effects were apparent. No adverse effects were observed at the lowest exposure level (NOAEL 696 mg/m^3).

In a set of long-term exposure studies, male Syrian hamsters (n = 35–36/group) were exposed to 0, 1,500 or 2,500/1,650 ppm (0, 2,679 or 4,464/2,946 mg/m^3) acetaldehyde for 7 hours/day × 5 days/week × 52 weeks (Feron 1979; Feron, Kruysse and Woutersen 1982). Due to extensive growth retardation, the exposure concentration was gradually decreased from 4,464 to 2,946 mg/m^3 during weeks 9 to 44 of the exposure period. At the lower exposure level, marked lesions were noted in the nasal cavity, including inflammation, keratinization, and squamous metaplasia; slight changes were noted in the tracheal tissues. The extent and severity of lesions were clearly diminished in animals allowed a 26-week recovery period. At the higher exposure level, lesions were also noted in nasal, tracheal, and laryngeal tissues; in contrast to the lower exposure level, after the recovery period, the lesions persisted.

5.2.2 Central nervous system effects

Ortiz et al. (1974) continuously exposed male T/O mice (n = 10) to acetaldehyde vapours for up to 10 days. At the start, exposure was 750 mg/m^3 and was gradually increased during the 10-day exposure period to 4,320 mg/m^3 acetaldehyde. Initially, mice demonstrated increased excitability (peak in activity at 30 minutes), followed by locomotor depression and ataxia; death was observed in 20% of the group by day 10. Analysis of brain tissue indicated an increase in monoamine neurotransmitters (noradrenaline, dopamine, and serotonin) with exposure. When exposure was withdrawn, a short transient increase in brain catecholamine was observed, with a return to baseline for all monoamine neurotransmitter concentrations six hours post-exposure. Mice exhibited excitation, tremor, piloerection, tail lift, and convulsions shortly after withdrawal, which persisted for two hours.

Shiohara et al. (1985) exposed male Sprague-Dawley rats (n = 6/group) to 0.3 mmol acetaldehyde/L air (13 mg/m^3) for (20 minutes × 4)/day for 2 to 21 weeks. Due to the rapid metabolism of acetaldehyde, short, repeated exposures were used to generate high blood levels of acetaldehyde. Acetaldehyde inhalation resulted in increased activity of Na^+, K^+-ATPase in the synaptosomal plasma membrane and microsomal fractions of cerebral cortex tissue, indicating a change in neural membrane function.

5.2.3 Immunological effects

Pulmonary allergic responses to ovalbumin were measured in non-sensitized and ovalbumin-sensitized male Hartley guinea pigs (n = 8/group) exposed to 0 or 200 ppb (0 or 0.4 mg/m^3) acetaldehyde for 6 hr/day x 5 days/week x 4 weeks (Lacroix et al. 2002). In both groups of guinea pigs, acetaldehyde exposure induced some irritation of the respiratory tract. Exposure to acetaldehyde did not potentiate the allergic or inflammatory responses to ovalbumin in the sensitized guinea pigs, compared to sensitization alone. In a study using mite allergen-sensitized BALB/c mice, Kawano et al. (2012) also noted that, while intranasal acetaldehyde (50 μg) alone did not trigger airway inflammation, it worsened airway hyperresponsiveness (as measured by a significant increase in specific airway resistance [sR_{aw}]).

Aranyi et al. (1986) evaluated host defense in female CD1 mice (n = 140–193/group) following inhalation of 0 or 200 ppm (0 or 357 mg/m^3) acetaldehyde for 3 hours/day × 5 days. Following acetaldehyde exposure, pulmonary bactericidal activity was reduced ($p < 0.05$), but mortality from streptococcal challenge was not different from controls.

5.2.4 Reproductive and developmental effects

Kruysse et al. (1975) evaluated the effect of subchronic acetaldehyde inhalation in Syrian golden hamsters (n = 40/sex/group). Hamsters were exposed to 0, 390, 1,340 or 4,560 ppm (0, 696, 2,393 or 8,143 mg/m^3) acetaldehyde 6 hours/day × 5 days/week for 90 days. Reduced ovary weight was only observed at 2,393 mg/m^3 (and not at the highest concentration) and increased testicular weight was noted at 8,143 mg/m^3.

No other studies of reproductive or developmental effects of acetaldehyde inhalation were identified in the literature. Developmental and fetotoxic effects of acetaldehyde have been demonstrated in animal studies primarily investigating the role of acetaldehyde as the metabolite of ethanol in fetal alcohol syndrome (WHO 1995; Environment Canada and Health Canada 2000). As these studies employed non-physiological routes of exposure (i.e. intraperitoneal, intravenous or amniotic injection), they were not considered in the derivation of an RIAQG.

5.2.5 Genotoxicity

Studies of the genotoxic and mutagenic properties of acetaldehyde have been extensively reviewed by a number of organizations, including the World Health Organization (1995), Environment Canada and Health Canada (2000), and the International Agency for Research on Cancer (1999). Acetaldehyde is largely negative in bacterial test systems, but has been demonstrated to be mutagenic in mammalian cells, to induce micronuclei formation in rat fibroblasts and human lymphocytes, to induce aneuploidy in Chinese hamster embryo cells and rat fibroblasts, to cause chromosomal aberrations in Chinese hamster cells and rat fibroblasts, and to cause sister chromatid exchange in Chinese hamster ovary cells, human lymphocytes and pre-implantation mouse embryos. In studies with laboratory animals, acetaldehyde exposure via intraperitoneal injection induced sister chromatid exchange in bone marrow cells of hamsters and mice, and increased the frequency of micronuclei formation in mouse erythrocytes.

In the single *in vivo* mutagenicity study identified (Kunugita et al. 2008), male C57BL/6 wild-type and ALDH2$^{-/-}$ mice (number of mice per group not reported) were exposed continuously to 0, 125 or 500 ppm (0, 223 or 893 mg/m^3) acetaldehyde vapour for two weeks. Mutagenicity, measured as an increase in micronucleus frequencies in reticulocytes and TCR gene mutations in T-lymphocytes, was observed at both exposure concentrations in the ALDH2$^{-/-}$ but not the wild-type mice ($p < 0.01$ and $p > 0.05$, respectively, as compared to ALDH2$^{-/-}$ air controls). In addition, at the 893 mg/m^3 exposure concentration, both measures of mutagenicity in the ALDH2$^{-/-}$ mice were also significant as compared to wild-type controls ($p < 0.05$), indicating a potential concentration–response relationship. This study suggests that although mutagenicity occurred in the absence of ALDH metabolism, it was not induced in the study when ALDH metabolism was active, even at relatively high acetaldehyde concentrations.

Further discussion on genotoxicity and mutagenicity (including information on DNA adducts and DNA–protein crosslinks) in the context of mode of action and relevance to acetaldehyde-induced nasal tumours can be found in Section 5.4.

5.2.6 Carcinogenicity

The carcinogenic effects of chronic inhalation of acetaldehyde have been evaluated in rats and Syrian golden hamsters (Feron 1979; Feron, Kruysse and Woutersen 1982; Woutersen et al. 1986).

These effects were evaluated in rats by Woutersen et al. (1986). Male and female Wistar rats (n = 55/sex/group) were exposed to 0, 750, 1,500 or 3,000/1,000 ppm (0, 1,339, 2,679 or 5,357/1,786 mg/m^3) acetaldehyde for 6 hours/day × 5 days/week for 28 months. Due to growth retardation, respiratory distress, weight loss, and mortality in the highest exposure group, the exposure concentration was gradually lowered to 1,786 mg/m^3 over 15 months. Significantly greater mortality was observed in the acetaldehyde exposure groups than the control group. At 102 weeks, all animals in the high exposure group had died, and by the end of the experiment, less than 20% of the 2,679 mg/m^3 group, 30% of the 1,339 mg/m^3 group, and 45% of the control group were still alive. Following interim euthanasia at 12 and 16 months of exposure, no statistically significant increase in tumour incidence in either male or female rats was observed, as compared to controls. The incidence of squamous cell carcinoma and adenocarcinoma in the nasal cavity of male and female rats at 20, 24, and 28 months is presented in Table 3, with statistical significance being reached for both males and females at varying concentrations and time points for both tumour types. Nasal carcinoma in situ was noted in some exposure groups, but did not reach a level of significance.

Feron et al. assessed these same effects in Syrian golden hamsters (Feron 1979; Feron, Kruysse and Woutersen 1982). In the 1979 study, male hamsters (n = 35/group) were exposed to 0 or 1,500 ppm (0 or 2,679 mg/m^3) acetaldehyde for 7 hours/day × 5 days/week × 52 weeks. Only non-neoplastic lesions developed in the respiratory tract at 2,679 mg/m^3 acetaldehyde. In the subsequent 1982 study, hamsters (n = 36/sex/group) were exposed to 0 or 2,500/1,650 ppm (0 or 4,464/2,946 mg/m^3) acetaldehyde for 7 hours/day × 5 days/week × 52 weeks followed by a 26-week recovery period. Due to extensive growth retardation, the exposure concentration was gradually decreased from 4,464 to 2,946 mg/m^3 during weeks 9 to 44. Non-neoplastic lesions were noted in the respiratory tract of hamsters exposed to 4,464/2,946 mg/m^3 acetaldehyde. The incidence of tumours in the larynx, including polyp/papilloma, carcinoma in situ, squamous cell

carcinoma, and adenosquamous carcinoma, was 6/23 ($p < 0.01$) for male hamsters and 4/20 for female hamsters (not statistically significant), while no tumours were noted in the control groups. Nasal tumours (2/27 for males and 1/26 for females) were detected in hamsters exposed to acetaldehyde; however, these incidences were not statistically significant.

Table 3. Cumulative incidence of tumours in the nasal cavity of Wistar rats (Woutersen et al. 1986)

Tumour type	Concentration (mg/m^3)	20 months	24 months	28 months
Males				
Squamous cell carcinoma	0	1/4	1/18	1/49
	1,339	0/7	1/24	1/52
	2,679	2/18	3/25	10/53*
	5,357/1,786	11/41	16/49	16/49***
Adenocarcinoma	0	0/4	0/18	0/49
	1,339	3/7	8/24*	16/52***
	2,679	13/18	16/25***	31/53***
	5,357/1,786	17/41	21/49***	21/49***
Females				
Squamous cell carcinoma	0	0/4	0/8	0/50
	1,339	0/6	0/15	0/48
	2,679	0/28	2/23	5/53
	5,357/1,786	10/41	17/53	17/53***
Adenocarcinoma	0	0/4	0/8	0/50
	1,339	2/7	5/15	6/48*
	2,679	11/11***	16/23**	28/53***
	5,357/1,786	13/34	23/53**	23/53***

Fisher exact tests: * $p<0.05$; ** $p<0.01$; *** $p< 0.001$

5.3 Summary of Health Effects

Based on the evidence from human and toxicological studies, the effects of short- and long-term acetaldehyde inhalation are observed at the site of entry. Key health effects include tissue damage and cancer development, mainly in the upper respiratory tract.

From the studies with human participants, acute exposure induced eye irritation at acetaldehyde concentrations as low as 25 ppm (45 mg/m^3), with nose and throat irritation reported at 50 to 200 ppm (89 to 357 mg/m^3) (Silverman, Schulte and First 1946). Acute exposure to lower concentration of acetaldehyde (22 mg/m^3) also potentiated the bronchoconstriction response to methacholine challenge (Myou et al. 1994a). At higher concentrations (350-1,000 mg/m^3), aerosolized acetaldehyde was shown to directly cause bronchoconstriction in people with asthma (Myou et al. 1993, 1994a, 1994b, 1995; Fujimura et al. 1997; Prieto et al. 2002a, 2002b). At an even higher concentration (2,100 mg/m^3), a bronchoconstrictive effect was induced in people with allergic rhinitis, while no effect was observed in healthy people at the highest exposure level tested (2,240 mg/m^3) (Prieto et al. 2002b). Epidemiological data on long-term effects in humans are limited to a single cross-sectional study of school children (Flamant-Hulin et al. 2010). A significant association between acetaldehyde exposure (measured in classrooms) and increased pulmonary inflammation was found for non-asthmatic children, but there was no association for asthmatic children; however, the results of this study may be impacted by limitations in the study design and analysis.

In laboratory animals, acute acetaldehyde exposure induced irritation and bronchoconstriction responses. For sensory irritation, measured as reduced respiration, the lowest RD_{50} was 2,845 ppm (5,080 mg/m^3) for a 10-minute exposure in mice (Steinhagen and Barrow 1984). Exposure at $\geq$ 25 ppm (45 mg/m^3) acetaldehyde in rats increased vasodilation in the upper respiratory tract, which may reflect a protective mechanism to irritant gases (Stanek et al. 2001).

In animal studies, long-term exposure to acetaldehyde caused inflammation and tissue injury, mainly in the upper respiratory tract. In rat studies, long-term acetaldehyde exposure caused adverse effects in the olfactory and respiratory epithelia of the nasal cavity, with tissue injury sometimes reported in the larynx, pharynx, and trachea, typically at higher exposure levels (Woutersen et al. 1984; Saldiva et al. 1985; Appelman et al. 1986; Woutersen et al. 1986; Woutersen and Feron 1987; Cassee et al. 1996; Cassee, Groten and Feron 1996; Oyama et al. 2007; Dorman et al. 2008). In these studies, the olfactory epithelium was the most sensitive tissue, with lesions noted at exposure concentrations as low as 268 mg/m^3 (Dorman et al. 2008). In hamster studies, tracheal and laryngeal tissues were more sensitive than the nasal cavity, although effects were observed at higher concentrations than in the rat studies (Kruysse, Feron and Til 1975; Feron 1979; Feron, Kruysse and Woutersen 1982), indicating a species-related difference. For both rats and hamsters, non-neoplastic tissue changes were largely concentration-dependent, and included inflammation, degeneration, hyperplasia, and metaplasia (Feron, Kruysse and Woutersen 1982; Woutersen et al. 1984; Woutersen et al. 1986; Woutersen and Feron 1987). In two mouse studies, reduced pulmonary bactericidal activity (Aranyi et al. 1986) and increased airway hyperresponsiveness (Kawano et al. 2012) were also observed. In some studies, growth retardation and mortality were observed at the highest exposure levels (4,464–8,929 mg/m^3) (Kruysse, Feron and Til 1975; Feron 1979; Feron, Kruysse and Woutersen 1982).

A small number of animal studies also reported transient changes in neurotransmitter levels as well as changes in neural membrane function in brain tissue (Ortiz, Griffiths and Littleton 1974; Shiohara et al. 1985), and altered gonad weight (Kruysse, Feron and Til 1975) following subchronic acetaldehyde inhalation exposure. In general, these effects were observed at greater exposure concentrations than were required to induce effects in the respiratory tract. Compared to effects in the upper respiratory tract, the database on these endpoints is limited.

Acetaldehyde is well demonstrated to be mutagenic and genotoxic in mammalian *in vitro* test systems (reviewed in WHO 1995; IARC 1999; Environment Canada and Health Canada 2000), as well as in an *in vivo* inhalation study in ALDH2 $^{-/-}$ mice (Kunugita et al. 2008). Acetaldehyde was not mutagenic in one *in vivo* study of mice with intact ALDH metabolism, but mutagenicity has not been extensively studied *in vivo*. Chronic inhalation exposure has caused carcinogenic effects in rats and hamsters at concentrations that induce tissue changes in the upper respiratory tract. Similar to the non-neoplastic effects, species-related differences in target tissue and sensitivity were evident. In rats, chronic exposure resulted in a concentration-dependent increase in adenocarcinoma of the olfactory epithelium and squamous cell carcinoma of the respiratory epithelium. Adenocarcinomas were more prevalent than squamous cell carcinomas and occurred at the lowest exposure level (1,339 mg/m^3) (Woutersen et al. 1986). In hamsters, chronic exposure at 4,464/2,946 mg/m^3 acetaldehyde resulted in a significant increase in tumour incidence of the larynx, while the incidence of nasal tumours did not reach significance (Feron 1979; Feron, Kruysse and Woutersen 1982).

Susceptible subpopulations

Studies of short-term exposures in human volunteers (reviewed in Section 5.1.1.1) provide evidence for asthmatics being a sensitive subgroup to inhaled acetaldehyde. Studies with Caucasian volunteers (Prieto et al. 2000; Prieto et al. 2002b) reported the greatest bronchoconstriction response in asthmatics, a lesser effect in people with allergic rhinitis, while no effect was observed in healthy subjects. A study with asthmatic and non-asthmatic Japanese volunteers also identified sensitivity to inhaled acetaldehyde only in the asthmatic group (Myou et al. 1993). It has been proposed that children, especially those with asthma, may be more likely to show adverse respiratory effects following exposure to acetaldehyde, due to higher prevalence rates of asthma in children as compared to other age groups, the small size of their airways, and the exacerbation that toxic air contaminants have been demonstrated to have on asthma in children (Delfino et al. 2003; CalEPA 2008).

As discussed in Section 4.1, an ALDH2 polymorphism in the human population greatly alters the rate of acetaldehyde metabolism, especially following alcohol consumption. The non-functional variant of ALDH2 (ALDH2-2) is prevalent in 40 to 50% of the Asian population, while it does not exceed 5% in Caucasian or African populations (Agarwal 2001; Druesne-Pecollo et al. 2009). In a study using Japanese asthmatics, Fujimura et al. (1999) did not observe a significant difference in hyperresponsiveness to inhaled aerosolized acetaldehyde in those with alcohol-sensitivity and those without. An upper respiratory tract PBPK model found minimal impact of the non-functional ALDH2-2 polymorphism, and ALDH2 was not considered a major contributor to acetaldehyde metabolism in the tissues (Teeguarden et al. 2008). In comparison, studies using ALDH2 $^{-/-}$ mice have reported an increased severity of treatment-related effects (i.e., severity of acute toxic effects, histological lesions, and DNA adduct formation in the upper respiratory tract following inhalation

exposure) in the knockout as compared to the wild-type mice (Isse et al. 2005; Oyama et al. 2007; Oyama et al. 2010). Overall, the ALDH2-2 variant may confer additional susceptibility to acetaldehyde toxicity following exposure, though this may depend on exposure concentration and duration.

5.4 Mode of Action for Carcinogenesis

A review of the health effects of inhaled acetaldehyde identified the nasal passage as the most sensitive tissue. Acetaldehyde is classified as possibly carcinogenic to humans by IARC (Group 2B), based on sufficient evidence of carcinogenicity in animals and inadequate evidence in humans (IARC,1999). Adenocarcinoma in the nasal cavity of male rats was the most sensitive chronic carcinogenic endpoint (observed at concentrations as low as 1,339 mg/m^3 in rats) (Woutersen et al. 1986). The most sensitive non-neoplastic chronic effects were also in the nasal passage (degeneration of the olfactory epithelium at 268 mg/m^3) (Dorman et al. 2008). Tumour development is likely related to occurrence of tissue damage and is dependent on saturation of acetaldehyde metabolism capacity, enhanced cellular proliferation, and mutation in the nasal cavity. This section presents plausible modes of action (MOAs) for nasal tumours resulting from inhalation exposure to acetaldehyde. A systematic MOA analysis was performed according to guidance set out in the International Life Sciences Institute/International Programme on Chemical Safety conceptual frameworks (IPCS 2007) and updated more recently (Meek, Palermo, et al. 2014; Meek, Boobis, et al. 2014); results of the analysis are summarized in this section. The weight of evidence points to a non-linear MOA for acetaldehyde carcinogenesis.

There is a high degree of similarity in formaldehyde and acetaldehyde carcinogenesis, including the critical key events in the MOA. An MOA evaluation of nasal cancer from long-term formaldehyde exposure has been proposed which identifies key events of sustained cytotoxicity, DNA–protein crosslink formation, and regenerative cell proliferation at the target site (McGregor et al. 2006). Neoplasia is proposed to result from genetic changes that are secondary to cytotoxicity, metaplasia, and hyperplasia. The response is non-linear, and mechanistic events of significance for carcinogenesis occur at concentrations where detoxification is saturated. Environment Canada and Health Canada (2001) similarly concluded that sustained cellular proliferation and interaction with genetic material contribute to the induction of nasal tumours, and the concentration–response relationships for formaldehyde-induced nasal cancer and associated intermediate endpoints appear to be non-linear. The assessment also noted that formaldehyde is weakly genotoxic and mutagenic, requiring high concentrations to induce mutations *in vitro* and limited evidence of mutagenesis *in vivo*.

Given that acetaldehyde has similarities in terms of structure and toxicity with formaldehyde, it is not unreasonable to contend that a similar, if not identical, MOA is at play for acetaldehyde-induced site-of-contact carcinogenesis. The pattern of genotoxicity and mutagenicity is consistent with a cytotoxic (secondary to a proliferative response), rather than mutagenic (critical early event) MOA for carcinogenesis. The following summarizes the hypothesized weight of evidence for the plausibility of these key events for acetaldehyde carcinogenesis.

5.4.1 Precursor event: Saturation of metabolic capacity for detoxification of acetaldehyde

A known precursor to cytotoxicity of formaldehyde is the saturation of metabolism, resulting in increased formaldehyde concentrations in the nasal tissues (McGregor et al. 2006). There is evidence that the toxic effects of acetaldehyde may also be due, in part, to an overwhelming of the acetaldehyde detoxification capacity at the site of exposure (discussed in Section 4.1). It has been demonstrated that acetaldehyde uptake, measured as upper respiratory tract deposition efficiency, decreases at elevated acetaldehyde exposure concentrations and is related to ALDH activity. Morris (1997) observed decreases in acetaldehyde uptake and an overwhelming of ALDH metabolic capacity for acetaldehyde at high concentrations (> 100 ppm [183 mg/m^3]). Further evidence for saturation of the ALDH metabolic pathway was provided by Stanek and Morris (1999) who observed a reduction in the percent uptake of acetaldehyde in rats at high concentrations (> 300 ppm [536 mg/m^3]), an effect that was prevented by exposure to an ALDH inhibitor, cyanamide. In addition, the toxicity of acetaldehyde has also been shown to be associated with ALDH activity. Studies using ALDH2$^{-/-}$ mice have reported an increased severity of acetaldehyde-induced toxic effects as compared to wild-type mice (Isse et al. 2005; Oyama et al. 2007; Oyama et al. 2010), providing support for saturation of detoxification capacity being a precursor for toxicity. Although a PBPK model (Teeguarden et al. 2008) predicted that acetaldehyde doses in nasal tissues increased linearly at air concentrations relevant to the rat studies (up to 5,000 ppm or 8,929 mg/m^3), non-linear increases in tissue proton (H^+) concentrations were observed in nasal tissues; increased acidification of nasal tissues might also be associated with cytotoxicity.

5.4.2 Key events 1 and 2: Cytotoxicity and subsequent enhanced cell proliferation in olfactory and epithelial tissues

As discussed below, the genotoxicity of acetaldehyde, as with formaldehyde, is linked to the induction of DNA damage during cell division. The carcinogenicity of acetaldehyde is proposed to be dependent on the induction of cytotoxicity, leading to increased cell turnover from recurrent tissue damage and repair. Increased cell proliferation results in a reduced time for effective DNA repair, and may enhance the likelihood that relevant DNA damage will lead to an increased chance of progression of pre-neoplastic cells to cancer.

Cytotoxicity (measured as degeneration of nasal tissues) was observed with concentration- and duration-related trends in rats, both within individual studies and when combining data from all studies. At the LOAEL of 150 ppm (268 mg/m^3) in rats, degeneration of olfactory tissues was observed in one study of up to 65 exposure days (Dorman et al. 2008). This effect was observed at higher concentrations in most other studies (Appelman, Woutersen and Feron 1982; Woutersen et al. 1984; Appelman et al. 1986; Woutersen and Feron 1987; Cassee et al. 1996) at durations as short as three days. The same effect in respiratory epithelium, which has higher ALDH activity (Bogdanffy, Randall and Morgan 1986), occurred only at ≥ 1,000 ppm (1,786 mg/m^3) (Appelman, Woutersen and Feron 1982; Woutersen et al. 1984; Dorman et al. 2008).

Enhanced cell proliferation in rat nasal tissues was observed either as hyperplasia or in assays measuring labelling index or unit length labelling index. The LOAEL for the effect in olfactory tissue of rats was 243 ppm (434 mg/m^3), which was observed after five weeks of exposure (Saldiva et al. 1985), with this effect also observed in studies with higher concentrations (Appelman,

Woutersen and Feron 1982; Woutersen et al. 1984; Woutersen et al. 1986; Woutersen and Feron 1987; Dorman et al. 2008). This effect was only observed at ≥ 500 ppm (893 mg/m^3) in respiratory tissues (Appelman, Woutersen and Feron 1982; Woutersen et al. 1986; Woutersen and Feron 1987; Dorman et al. 2008). Enhanced cell proliferation was also observed in a study following administration in drinking water. Oral exposure of Wistar rats to a single concentration of acetaldehyde in drinking water (120 mM [324 mg/kg bw/day]) resulted in increased cell proliferation of the tongue, epiglottis, and forestomach (Homann et al. 1997).

5.4.3 Key events 3 and 4: Development of DNA adducts and DNA–protein crosslinks, and mutations in olfactory and epithelial tissues

Acetaldehyde has been shown to induce DNA damage in the form of DNA adducts, DNA–DNA crosslinks, DNA–protein crosslinks as well as more complex adducts (reviewed in Albertini 2013), events that, under certain conditions, lead to mutations. DNA–DNA and DNA–protein crosslinks can also interrupt DNA replication, repair, recombination, and transcription as well as chromatin remodelling. Acetaldehyde has also been shown to be an indirect-acting genotoxin in that it is capable of generating oxidative damage, resulting in the formation of 8-oxo-dG adducts, a biomarker of oxidative DNA damage, *in vitro* and *in vivo* (Ogawa et al. 2006). In *in vitro* studies involving mammalian cells, positive mutagenic results have been observed at high exposure concentrations, while tumours occur in rodents at the site of contact following high exposure concentrations and are associated with tissue damage (Albertini 2013).

5.4.3.1 DNA adducts

The electrophilic nature of the carbonyl carbon of acetaldehyde results in reactions with DNA, generating DNA adducts. The main reactions occur with deoxyguanosine (dG), followed by deoxyadenosine, and then deoxycytosine . The most abundant and well-studied acetaldehyde–DNA adduct is N^2-ethylidene-dG, which can be stabilized by reduction to N^2-ethyl-dG (Balbo and Brooks 2015), followed by N^2-propano-deoxyguanosine (PdG) (Garcia et al. 2009; Albertini 2013). The PdG adduct can exist in two forms (ring-open and ring-closed); it is the ring-open form that permits the formation of DNA–DNA and DNA–protein crosslinks (Brooks and Theruvathu 2005) (Figure 3B). PdG adducts, when left unrepaired, have a well-recognized mutagenic potential (Albertini 2013), while the instability of N^2-ethylidene-dG prevents direct investigation of its biological properties.

Increased N^2-ethylidene-dG DNA adduct formation (measured as its reduced form, N^2-ethyl-dG) was reported in nasal, lung, and dorsal skin tissue of male wild-type and ALDH2$^{-/-}$ mice (n = 7-10/group) continuously exposed to 125 and 500 ppm (223 and 893 mg/m^3) acetaldehyde for 14 days (Oyama et al. 2010). For both mouse strains, the highest levels of DNA adducts were observed in the nasal epithelium; however, greater adduct formation was noted in the ALDH2$^{-/-}$ strain compared to wild-type mice, indicating an increased sensitivity to adduct formation with ALDH2 deficiency.

Exogenous and endogenous N^2-ethyl-dG DNA adducts have been observed in human lymphoblastoid TK6 cells following exposure to isotopically labeled (^{13}C) acetaldehyde (Moeller et al. 2013). While endogenous adduct levels were relatively constant across all exposure concentrations, exogenous adducts increased in a concentration-dependent manner, with two

distinct linear regions. Below 50 μM, exogenous adduct formation increased at a slower rate than at higher concentrations (250–2,000 μM). Moreover, a clear threshold for N^2-ethyl-dG formation was observed (at 50 μM), based on the sum of endogenous and exogenous adducts. Analysis of the concentration–response curve revealed two distinct regions, with a higher rate of formation of adducts observed at higher concentrations. In the same study, concentration-dependent increases in micronuclei were observed, with a clear threshold of effect identified at 2,000 μM.

Supporting evidence for the DNA damaging capabilities of acetaldehyde is also found from studies of the effects of alcohol on DNA adducts (reviewed in Albertini 2013).

5.4.3.2 DNA–protein and DNA–DNA crosslinks

Acetaldehyde induces DNA–protein crosslinks *in vitro* (reviewed in Brooks and Theruvathu 2005). A small number of studies have also observed DNA–protein crosslinks following inhalation exposure to acetaldehyde, even though some studies have failed to demonstrate this effect.

The lowest concentration at which DNA–protein crosslinks were measured in rat nasal mucosa (both olfactory and respiratory epithelium) was 1,000 ppm (1,786 mg/m^3); however, results were not consistent among studies. Lam et al. (1986) reported decreased extractability of DNA from insoluble proteins (an indirect measure of DNA–protein crosslink formation) at acetaldehyde concentrations of 1,000 and 3,000 ppm (1,786 and 5,358 mg/m^3) after five days in both tissues, and after one day in the respiratory epithelium alone (but not after 100 or 300 ppm [179 or 536 mg/m^3] for either duration). Conversely, Dorman et al. (2008) did not report an increase in DNA–protein crosslinks in either the olfactory or respiratory epithelium of rats exposed to 150, 500 or 1,500 ppm (268, 893 or 2,679 mg/m^3) acetaldehyde for 4 to 65 exposure days. Moreover, Stanek and Morris (1999) did not detect an increase in DNA–protein crosslinks in respiratory mucosa of male F344 rats exposed to 2,679 mg/m^3 acetaldehyde for a single six-hour exposure. Note, however, that these two studies used a different method for detection of DNA–protein crosslinks compared to Lam et al (1986), which may explain the contrasting results between the studies. Stanek and Morris (1999) and Dorman et al. (2008) employed a method based on sodium dodecyl sulfate-potassium chloride binding, while Lam et al. (1986) used a phenol–chloroform DNA extraction followed by analysis of the proportion of interfacial DNA.

Acetaldehyde has been shown to induce DNA–DNA crosslinks *in vitro*, in human peripheral blood lymphocytes (Lambert et al. 1985). Exposure of human lymphocytes, gastric mucosal cells or colonic mucosal cells to acetaldehyde has been shown to cause a reduction in DNA fragmentation in the alkaline comet assay, compared to control of ethanol-exposed cells, an observation attributed to the induction of DNA–DNA crosslinks (Blasiak et al. 2000).

Garcia et al. (2009) compared the relative formation of DNA–protein crosslinks following acetaldehyde, formaldehyde and mitomycin-C exposure in Chinese hamster ovary cells, employing a modified version of the comet assay that uses proteinase K to differentiate between DNA interstrand (DNA–DNA) crosslinks and DNA–protein crosslinks. As with formaldehyde, they observed a concentration-dependent increase in acetaldehyde-induced DNA–protein crosslinks. This confirms that acetaldehyde predominantly induces DNA–protein crosslinks, rather than DNA interstrand crosslinks, such as those formed by mitomycin-C.

As no studies have investigated mutagenic outcomes of acetaldehyde in rat nasal tissues after *in vivo* exposure, this key event cannot be assessed quantitatively in comparison with other key events in the same tissues. However, the occurrence of mutations in rats is likely. In a mouse study, mutagenicity was demonstrated in ALDH2$^{-/-}$ but not wild-type mice exposed to acetaldehyde vapour (Kunugita et al. 2008), supporting the importance of saturation of the metabolic capacity for detoxification of acetaldehyde as a key initial step in the tumourigenic process.

5.4.4 Key event 5: Development of tumours in nasal olfactory and respiratory tissues

Carcinogenicity studies conducted in rats (Woutersen et al. 1984; Woutersen et al. 1986; Woutersen and Feron 1987) and hamsters (Feron, Kruysse and Woutersen 1982) observed lesions of the respiratory tract and development of tumours. The reports by Woutersen et al. (1984, 1986, 1987) indicated a concentration-dependent response for both cell degeneration and tumour development, at all concentrations of acetaldehyde evaluated. Interim evaluation of the exposed rats indicated tumour development after 12 months of exposure (earliest time point evaluated). Therefore, the concurrent observations of tissue damage and tumour development preclude identification of a temporal difference (i.e., tissue damage is a necessary step prior to tumour development). In a chronic exposure study with hamsters, Feron (1979) reported lesions of the respiratory tract in the absence of tumour development; in a subsequent study, Feron, Kruysse and Woutersen (1982) observed both lesions and tumour development at a high exposure level. The respiratory tract was the main site of effect for all species of laboratory animals tested.

The site-specific carcinogenic response supports the proposed non-linear MOA for carcinogenesis. A species difference was noted as in rats the tumours were mainly observed in nasal tissues, while in hamsters a majority of tumours were located in the larynx. This may be due to differences in metabolism in the different tissue types, differential susceptibility, and/or differences in anatomy and breathing pattern. Overall, the evidence demonstrates that acetaldehyde has the potential to act via a cytotoxic mechanism, with mutagenicity and tumour formation occurring secondary to saturation of metabolic capacity and subsequent tissue damage and cell proliferation.

5.4.5 Concordance of concentration–response and temporal association

A consistent concentration–response effect for respiratory tract epithelium degeneration has been demonstrated in studies in rats, mice, and hamsters (Kruysse, Feron and Til 1975; Feron 1979; Appelman, Woutersen and Feron 1982; Feron, Kruysse and Woutersen 1982; Woutersen et al. 1984; Appelman et al. 1986; Woutersen et al. 1986; Woutersen and Feron 1987; Cassee et al. 1996; Oyama et al. 2007; Dorman et al. 2008) at acetaldehyde concentrations that have been proposed to exceed ALDH metabolic capacity (Morris 1997; Stanek and Morris 1999). Cell proliferation tended to occur at higher concentrations than cytotoxicity, and both of these key events occurred at lower concentrations than the LOAELs for tumours. The earlier key events also occur after shorter durations than later key events, as would be expected. The formation of DNA–protein crosslinks in nasal tissue was less consistently reported in the literature and only occurred at concentrations higher than those resulting in tumours. Lam et al. (1986) and Oyama et al. (2010) reported crosslink formation in nasal tissue following exposures of a few hours to 14 days; however, crosslinks were not detected by Stanek and Morris (1999) following a 6-hour exposure or by Dorman et al. (2008) in a 13-week exposure (65 exposure days). There is a possibility,

however, that this discrepancy is due to methodological differences between the studies. Moreover, regenerative cell proliferation could result in the propagation of other types of DNA damage, either acetaldehyde-induced or spontaneous mutations; if this occurs, the development of mutations due to DNA–protein crosslinks might not be a necessary step for tumour development. In an *in vitro* rodent study, mutagenicity was demonstrated in ALDH2$^{-/-}$ but not wild-type mice exposed to acetaldehyde vapour (Kunugita et al. 2008), supporting the importance of saturation of the metabolic capacity for detoxification of acetaldehyde as a key initial step in the tumourigenic process.

Observation of the effects in different tissues also supports concentration–response concordance. In rats, ALDH activity is much higher in epithelial cells of the respiratory mucosa than in those of the olfactory mucosa, where activity is weak to non-existent (Bogdanffy, Randall and Morgan 1986). The LOAELs for most key events occur at lower concentrations in olfactory tissue than respiratory tissue, as would be expected because of the higher ALDH activity in the latter tissue. One discrepancy is that the generation of DNA–protein crosslinks was observed at the same concentrations in the two tissues, although at an earlier time point in the respiratory tissues. However, as discussed earlier, the relevance of DNA–protein crosslink development on tumourigenicity is not clear; studies that investigate the ability of acetaldehyde to propagate spontaneous mutations might also need to be considered. The effect of acetaldehyde on gastrointestinal tissues after oral exposure also provides some support for the susceptibility of portal-of-entry tissues. Increased cell proliferation was observed in upper gastrointestinal tract tissues of rats (Homann et al. 1997), and acetaldehyde is suspected as a potential contributor to alcohol-induced tumours in the gastrointestinal tract (Seitz and Homann 2007; Seitz and Meier 2007).

5.4.6 Human relevance

Only two epidemiological studies of inhalation exposure to air pollutants (including acetaldehyde) or a mixture of aldehydes were identified (IARC 1999; Flamant-Hulin et al. 2010). Nevertheless, it is likely that this cancer MOA is relevant to humans, based on the data available for each key event (as presented below).

Precursor: It is reasonable to assume that saturation of ALDH-mediated acetaldehyde metabolism is relevant to humans, as ALDH is expressed in both rodent and human tissues. Rat and human ALDH activities (i.e., K_m values) are also equivalent (Bogdanffy et al. 1998).

Key events 1 and 2: It is reasonable to assume that the cytotoxicity and enhanced cell proliferation response is relevant to humans, as the cellular damage and regenerative proliferation response to toxic insult is not expected to be, at least qualitatively, different between rodents and humans. In addition, the contribution of tissue acidification to cytotoxicity is not expected to differ between rats and humans.

Key events 3 and 4: It is reasonable to assume that mutations resulting from interactions with DNA are relevant to humans. Acetaldehyde has been shown to induce genetic damage (micronuclei and sister chromatid exchange) in human lymphocytes *in vitro* as well as DNA adducts and DNA–DNA crosslinks in human cells *in vitro*. It is reasonable to assume that these effects will also manifest *in vivo*.

Key event 5: The development of respiratory tumours as a result of cytotoxicity and subsequent regenerative proliferation is plausible in humans. Many different cancers in humans are thought to arise from sustained regenerative cellular proliferation, including those in lung tissues (Grasso, Sharratt and Cohen 1991). Moreover, adenocarcinomas and squamous cell carcinomas—the nasal tumours observed in rat studies—are both tumours that can arise in the upper respiratory tract in humans (Woutersen, Kuper and Slootweg 2010). Finally, sufficient evidence exists to conclude that sinonasal tumours in humans can be induced by high concentrations of formaldehyde, for which a strong weight of evidence exists for the cytotoxicity MOA (McGregor et al. 2006).

As ALDH activities are similar among rats and humans (Bogdanffy et al. 1998; Teeguarden et al. 2008), the MOA is also considered to be quantitatively relevant to humans.

5.4.7 Confidence in the proposed MOA

Based on the considerations presented above, the proposed carcinogenic MOA in humans is highly relevant. A greater weight of evidence exists for the MOA discussed above than a MOA for direct mutagenicity. Although data indicate that acetaldehyde exposure does result in DNA–protein crosslink formation in rat nasal tissues, quantitative data do not indicate that this event precedes cell replication. As discussed in the cytotoxicity MOA, cellular proliferation has been observed at concentrations as low as 243 ppm (434 mg/m^3), whereas the development of DNA–protein crosslinks was not observed at 300 ppm (536 mg/m^3). However, a weakness in the dataset is that DNA–protein crosslinks were only measurable in one study.

Indirect genotoxicity due to oxidative DNA damage is another MOA that could be relevant to the tumourigenic effects of acetaldehyde. Insufficient data exist to assess oxidative DNA damage as an early key event in tumours in rats. Some evidence of oxidative DNA damage exists in mice—Ogawa et al. (2006) identified increased levels of urinary 8-hydroxydeoxyguanosine (8-OHdG), a biomarker of oxidative DNA damage, after 6 and 12 days of continuous exposure to 500 ppm acetaldehyde (893 mg/m^3). However, the absence of tumour data in mice precludes the ability to assess the relevance of this effect to acetaldehyde-induced tumourigenesis. An MOA involving oxidative DNA damage might not be completely separate from a cytotoxic MOA; oxidative stress could be involved in the cytotoxic response. Further research would need to be performed before oxidative DNA damage is considered as part of the MOA for acetaldehyde.

As discussed below, in the previous Government of Canada acetaldehyde assessment (Environment Canada and Health Canada 2000), a linear multistage model with adjustment for continuous exposures was used to calculate a value of 17.2 µg/m^3 for a 1 in 100,000 cancer risk level. It was recognized that the greatest source of uncertainty in the assessment was the carcinogenic MOA of acetaldehyde, although it was proposed that cytotoxicity as well as genotoxicity of acetaldehyde has a critical role in the carcinogenicity of this compound. Overall, comprehensive reviews published prior to this Government of Canada assessment utilized linear multistage models to quantify cancer risk, with the exception of the World Health Organization (1995) who developed tolerable concentrations (TCs) for acetaldehyde carcinogenesis using both linear and non-linear approaches. More recent literature—such as data involving ALDH knockout mice, supporting the critical role of ALDH2 saturation and cytotoxicity in the site-of-contact

carcinogenesis, and key genotoxicity and mutagenicity studies—has provided support for the non-linear rather than the previously considered linear MOA for the carcinogenicity of acetaldehyde.

In addition to the previously discussed support that the formaldehyde MOA provides, supporting evidence for the MOA of acetaldehyde site-of-contact carcinogenesis can also be found from the weight of evidence for vinyl acetate MOA (Environment Canada and Health Canada 2008). IARC (1995) has classified vinyl acetate as a Group 2B carcinogen (possibly carcinogenic to humans). This classification was based on the rapid transformation of vinyl acetate into acetaldehyde in human blood and animal tissues, the existence of sufficient evidence for the carcinogenicity of acetaldehyde in experimental animals, the evidence for *in vivo* and *in vitro* genotoxicity, and the induction of nasal tumours in rats by both acetaldehyde and vinyl acetate. In a review of the MOA for vinyl acetate carcinogenicity in their risk assessment report, Environment Canada and Health Canada (2008) proposed the existence of a threshold for vinyl acetate carcinogenicity. The MOA for vinyl acetate requires an initial cytotoxic event, followed by concurrent cell proliferation and genotoxicity by acetaldehyde (specifically DNA–protein crosslinks).

It is recognized that there is some uncertainty regarding the shape of the concentration–response curve, particularly at lower concentrations (i.e., concentrations below which cytotoxic effects were observed). Additional information on effects at low concentrations (e.g., information on metabolic capacity/ALDH saturation at low concentrations) would alleviate this uncertainty, but would not alter the overall MOA.

6.0 DERIVATION OF SHORT- AND LONG-TERM REFERENCE CONCENTRATIONS

6.1 Short-term reference concentration

For short-term exposure to acetaldehyde, several studies investigating the bronchoconstriction response in human volunteers were identified in the literature (see Section 5.1.1.1), with aerosolized exposure concentrations ranging from 0.04 to 80 mg/mL (1.12 to 2,240 mg/m^3). In these studies, asthmatic subjects had the greatest responsiveness to acetaldehyde, as reflected by the lowest PC_{20} measurements. Among the acute exposure studies with human volunteers, Prieto et al. (2000) was identified as the key study, having the largest sample size of asthmatic participants (61 subjects compared to 9–16 subjects in other short-term exposure studies). The larger sample size would be expected to better describe the central tendency given the large interindividual variability observed in the studies. Also, the model of nebulizer used in the studies by Fujimura et al. (1997, 1999) and Myou et al. (1994a, 1994b, 1995) has been demonstrated to have inconsistent output and delivery, which could impact the accuracy of the measurements obtained in these studies (Hollie et al. 1991).

From Prieto et al. (2000), the PC_{20} geometric mean for asthmatic subjects was 17.55 mg/mL acetaldehyde following a two-minute exposure. The 95% confidence interval of the geometric mean was 4.72 to 38.3 mg/mL (CalEPA 2008). This corresponds to an acetaldehyde concentration in air of 527 mg/m^3 (95% CI: 142–1,149 mg/m^3). The lower 95% confidence interval of 142 mg/m^3 was chosen as the point of departure, and uncertainty factors (UFs) of 10 to account for

the use of a LOAEL and 10 for additional sensitivity in the human population (e.g., more severe asthmatics, children, ALDH polymorphisms) were applied. A detailed justification for the selection of UFs for both short- and long-term reference concentrations (RfCs) can be found in the report from Ritter et al. (2007). Thus, the short-term RfC is 1,420 $\mu g/m^3$.

Silverman et al. (1946) reported sensory irritation in some study participants at 25 ppm (45 mg/m^3) and Myou et al. (1994b) reported that acetaldehyde (22 mg/m^3) potentiated the bronchoconstriction response to methacholine. The study by Silverman et al. (1946) was not chosen for the derivation of the short-term RfC due to a small sample size, non-quantitative measures of irritation, and issues with the experimental procedure. A short-term RfC of 1,420 $\mu g/m^3$ is anticipated to also be protective of these effects.

6.2 Long-term reference concentration

Inhalation studies in laboratory animals have demonstrated neoplastic effects with longer term exposures; however, these are inextricably linked with non-neoplastic effects. A strong body of evidence has also emerged to support the notion that acetaldehyde exerts its carcinogenic effect through a non-linear MOA (reviewed in Section 5.4).

The most sensitive chronic neoplastic endpoint was adenocarcinoma in the nasal cavity of male rats. For non-neoplastic effects, the most sensitive endpoint was degeneration of the olfactory epithelium in rats. As the MOAs for the neoplastic and non-neoplastic effects of acetaldehyde are related, derivation of an RfC for the neoplastic effects is based upon consideration of the non-neoplastic effects, precursors to the carcinogenic response. The most appropriate study for the selection of a point of departure was that of Dorman et al. (2008), where rats were exposed to acetaldehyde for longer duration (13 weeks, up to 65 exposure days) and at lower concentrations (0, 89, 268, 893 or 2,679 mg/m^3) than in previous studies (Appelman, Woutersen and Feron 1982; Appelman et al. 1986). From this study, a NOAEL of 89 mg/m^3 is identified, based on degeneration of the olfactory epithelium. Using the PBPK model for acetaldehyde inhalation (Section 4.2), the HEC is 120 mg/m^3. Adjusting this value for exposure duration from the animal study (6 hours/day × 5 days/week) to a continuous exposure (24 hours/day × 7 days/week) results in an adjusted HEC of 21 mg/m^3. Uncertainty factors of 2.5 to account for toxicodynamic differences between animals and humans, and 10 for additional sensitivity in the human population were applied. A UF of 3 was also applied to account for uncertainty in the shape of the lower region of the concentration–response curve (i.e., concentrations where only non-neoplastic effects occur) (Ritter et al. 2007). This results in a total UF of 75. Thus, the long-term RfC is 280 $\mu g/m^3$.

6.3 Exposure in Canadian homes in relation to reference concentration and determination of RIAQGs

In the past decade, Health Canada has completed several exposure studies in multiple Canadian cities. These studies are considered the most recent and most representative data available for quantifying long-term levels of exposure in Canadian homes (see Section 3.0).

Short- and long-term RfCs are based on the characterization of the concentration–response relationship and the application of UFs to account for variability and data gaps. The context within which these RfCs are to be applied, technical feasibility, and availability of risk mitigation

measures do not enter into their determination. However, these issues are relevant to the determination of short- and long-term RIAQGs.

In order to determine the proposed RIAQG exposure limits, the short- and long-term RfCs are first compared to available exposure data from Canadian homes. The feasibility of achieving the RfC through the control of indoor sources is then evaluated. If the RfC is judged to be feasible, the same value is set as the RIAQG. If not, a higher concentration may be selected, while still targeting an exposure limit that is protective of health in consideration of current evidence.

In the present assessment, the criteria guiding the determination of the value for both the proposed short- and long-term RIAQGs for acetaldehyde are:

- a value that is generally achievable in Canadian homes in the absence of significant source of indoor acetaldehyde; and
- a value that is not associated with appreciable health effects, considering the derived reference exposure levels and currently available evidence.

6.3.1 Short-term reference concentration and RIAQG

The literature database provided sufficient information on the effects in humans for development of a short-term RfC, which was determined for acetaldehyde to be 1,420 $\mu g/m^3$. The range of median indoor air acetaldehyde concentrations measured in Canadian homes from the Health Canada residential indoor air exposure studies for a 24-hour averaging period was 10.5 to 48.7 $\mu g/m^3$, with the 95th percentile ranging from 35.6 to 149.5 $\mu g/m^3$ (see Table 2). The 24-hour integrated samples collected in these studies do not represent acute or peak exposures. However, short-term acetaldehyde peaks likely occur with the use of fireplaces, wood-burning stoves, and some consumer products as well as behaviours such as smoking, cooking or conducting home renovations. Based on the 24-hour sampling data and the expected sources present, it is expected that the short-term RfC is achievable in Canadian homes. Therefore, the proposed short-term RIAQG for acetaldehyde is 1,420 $\mu g/m^3$.

6.3.2 Long-term reference concentration and RIAQG

From the literature database, a chronic RfC of 280 $\mu g/m^3$ was derived based on degeneration of the olfactory epithelium. This RfC is considered to be protective of both neoplastic and non-neoplastic effects. The Health Canada residential indoor air exposure studies provide the best measure of chronic exposure in Canadian homes. The range of median indoor air acetaldehyde concentrations measured in Canadian homes for a 24-hour averaging period was 10.5 to 48.7 $\mu g/m^3$, with the 95th percentile ranging from 35.6 to 149.5 $\mu g/m^3$ (see Table 2). This indicates that Canadian homes would not exceed the RfC of 280 $\mu g/m^3$; therefore, this value is retained as the long-term RIAQG. Therefore, the proposed long-term RIAQG for acetaldehyde is 280 $\mu g/m^3$.

6.4 Uncertainties and areas of future research

For health effects in humans, the literature database is most developed for short-term acetaldehyde exposures, while limited information is available on longer exposure durations. Additionally, there is some information on the acute health effects in sensitive populations, such as those with asthma

or carrying the ALDH2-2 polymorphism. However, the magnitude and occurrence of the increased sensitivity are not fully understood and have not been fully evaluated with respect to longer exposure durations.

Most health effects research has primarily focused on respiratory effects and, to a lesser extent, on carcinogenicity. In comparison, very few studies have reported cardiovascular, neurological, immunological, or reproductive and developmental effects associated with acetaldehyde inhalation. The cancer risk at low exposure concentrations (i.e., levels that do not cause cytotoxicity) has not been investigated. Addressing the main uncertainty of the long-term RfC developed in this assessment (i.e., the shape of the concentration-response curve) would result in a clearer understanding of cancer risk at low concentrations (i.e., environmentally relevant concentrations). This could be achieved by performing similar modelling and analysis carried out for formaldehyde.

Existing exposure studies have evaluated 24-hour and 5-day sampling times, as these provide the best estimates of average daily exposures. Exposures to peak concentrations during shorter durations have not been evaluated.

With respect to sources of acetaldehyde in the indoor environment, the contribution from different potential sources (e.g., building materials vs. flooring materials vs. consumer products) is not well understood.

7.0 PROPOSED GUIDELINES

Table 4. Proposed acetaldehyde guidelines for indoor environments

Exposure Limit	Concentration		Critical effect(s)
	µg/m³	ppb	
Short-term (1 h)	1,420	795	Increased airway responsiveness in asthmatics
Long-term (24 h)	280	157	Olfactory epithelial degeneration in the nasal cavity of rats

7.1 Sampling times

It is recommended to compare the short-term exposure limit to a one-hour air sample.

When comparing a measured acetaldehyde concentration with the long-term exposure limit, the sampling time should be at least 24 hours, taken under normal conditions. Moreover, the averaging of results of repeated samples taken at different times of the year will provide a more representative estimate of long-term exposure.

7.2 Risk management recommendations

Most homes in Canada have levels of acetaldehyde below the long-term exposure limit derived for protection against nasal epithelium cytotoxicity and carcinogenicity. Regardless, sources of acetaldehyde in the homes should be controlled to limit exposure as much as reasonably possible, given that air quality testing in individual homes is neither practical nor recommended in most instances. Furthermore, many of the measures outlined below will also contribute to reducing the concentrations of other indoor air contaminants, generally improving indoor air quality.

Strategies for reducing exposure to acetaldehyde include controlling indoor emissions from combustion appliances and smoking. Control measures include the following:

- not smoking inside the home;
- properly install and maintain combustion appliances used for heating (e.g., gas and oil furnaces, wood stoves, gas water heaters), with venting outside; and
- use a higher fan setting when cooking on a gas stove, ensure that it vents outside, and preferentially use the back burners.

Consumer products such as paints, adhesives, coatings, lubricants, inks, nail polish remover, and fragrances should be kept well sealed and/or in non-occupied areas of the home not connected to the ventilation system, where possible. When applying adhesives, coatings, etc. in the home or performing home renovations, including installation of carpeting or vinyl flooring, the area should be well ventilated, and the user should follow all label recommendations.

If these products are stored in attached garages, actions should be taken to prevent air leakage from the attached garage into the house and to make sure that there is an appropriate seal between the home and the garage, particularly for any door that connects the two areas. This can be achieved by providing an appropriate air barrier and a sealed door between the garage and house and drywalling shared walls between the garage and house. These actions will also reduce the air exchange between the home and the garage.

8.0 REFERENCES

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APPENDIX A: HUMAN EXPOSURE STUDIES

A1. Short-term Exposure

Study	Participants	Exposure	Results	NOAEL/LOAEL
Muttray et al. 2009	Healthy males (n = 20)	89 mg/m^3 acetaldehyde or air exposure for 4 h	No subjects reported irritation, no change in olfactory threshold, and no inflammation in the upper airways	NOAEL: 89 mg/m^3 LOAEL: not determined
Sim and Pattle 1957	Healthy males (n = 14)	239 mg/m^3 acetaldehyde for 30 min	Mild irritation of the upper respiratory tract	NOAEL: not determined LOAEL: 239 mg/m^3
Silverman, Schulte and First 1946	Healthy males and females (n = 12/sex)	0, 45, 89, and 357 mg/m^3 acetaldehyde for 15 min	Several subjects exhibited eye irritation at 45 mg/m^3. Most subjects reported eye irritation at 89 mg/m^3. Nose and throat irritation in majority of subjects at 357 mg/m^3.	NOAEL: not determined LOAEL: 45 mg/m^3

A2. Bronchoconstriction Studies

Study	Participants	Exposure	Results	PC20 (mg/m^3)
Fujimara et al. 1999	Japanese asthmatic males and females with alcohol sensitivity (n = 10) and without alcohol sensitivity (n = 16) Mild, stable asthma with use of β_2-agonists and/or oral theophylline (no steroid use for 8 wk); 24-h washout	2-min inhalation by mouth of 0.04, 0.08, 0.16, 0.31, 0.63, 1.25, 2.5, 5, 10, 20, 40, and 80 mg/mL acetaldehyde (corresponds to 1.12, 2.24, 4.48, 8.68, 17.64, 35, 70, 140, 280, 560, 1,120, and 2,240 mg/m^3)	Alcohol sensitive group: PC_{20} = 21.0 mg/mL (STGM of 0.112) corresponds to 588 mg/m^3 acetaldehyde in air Alcohol insensitive group: PC_{20} = 31.7 mg/mL (STGM of 0.077) corresponds to 888 mg/m^3 acetaldehyde in air	Alcohol sensitive group: 588 Alcohol insensitive group: 888

Myou et al. 1993	Japanese asthmatic males (n = 9) Japanese healthy males (n = 9) Mild, stable asthma with use of β_2-agonists, oral theophylline, and/or mucolytic agents (no steroid use for 8 wk); 18 h washout	2-min inhalation by mouth of 5, 10, 20, and 40 mg/mL acetaldehyde (corresponds to 140, 280, 560, and 1,120 mg/m^3)	A concentration-dependent decrease in FEV_1 was noted in asthmatic subjects. No significant decrease was observed in healthy subjects or asthmatic subjects pre-treated with a histamine blocker. PC_{20} = 20 mg/mL corresponds to 560 mg/m^3 acetaldehyde in air	560
Myou et al., 1994a	Japanese asthmatic males and females (n = 9) Mild, stable asthma with use of β_2-agonists and/or oral theophylline (no steroid use for 8 wk)	4-min inhalation by mouth of 5, 10, 20, and 40 mg/mL acetaldehyde (corresponds to 140, 280, 560, and 1,120 mg/m^3) Methacholine challenge: 4-min inhalation of 0.8 mg/mL acetaldehyde (corresponds to 22.4 mg/m^3)	PC_{20} = 23.3 mg/mL (range 12.8 to 38.4 mg/mL) corresponds to 652 mg/m^3 acetaldehyde in air Acetaldehyde increased responsiveness to methacholine challenge ($p < 0.05$); pre-treatment with a histamine blocker did not suppress the potentiation.	652
Myou et al., 1994b	Japanese asthmatic males and females (n = 9) Mild, stable asthma with use of β_2-agonists and/or oral theophylline (no steroid use for 8 wk)	2-min inhalation by mouth of 5, 10, 20, and 40 mg/mL acetaldehyde (corresponds to 140, 280, 560, 1,120 mg/m^3)	PC_{20} = 19.8 mg/mL (STGM of 1.2) corresponds to 554 mg/m^3 acetaldehyde in air Pre-treatment with OKY-046 (thromboxane synthetase inhibitor) significantly increased the PC_{20} of acetaldehyde	554
Myou et al. 1995	Japanese asthmatic males and females (n = 9) Mild, stable asthma with use of β_2-agonists and/or oral theophylline (no steroid use for 8 wk); 24 h washout	Repeated (1 h interval) 2-min inhalation by mouth of 0.04, 0.08, 0.16, 0.31, 0.63, 1.25, 2.5, 5, 10, 20, 40, and 80 mg/mL acetaldehyde (corresponds to 1.12, 2.24, 4.48, 8.68, 17.64, 35, 70, 140, 280, 560, 1,120, and 2,240 mg/m^3)	Initial PC_{20} = 18.4 mg/mL (STGM of 0.14) corresponds to 510 mg/m^3 acetaldehyde in air 1 h PC_{20} = 45.2 mg/mL (STGM of 0.14) corresponds to 1266 mg/m^3 acetaldehyde in air Increased PC_{20} on re-challenge indicated tachyphylaxis to acetaldehyde	510

Prieto et al. 2000	Caucasian asthmatic males and females (n = 61) Caucasian healthy males and females (n = 20) Asthmatics had no oral corticosteroid use for 2 mo prior, no inhaled corticosteroid use for 4 wk prior, maintenance medication withheld for 24 h, β_2-agonists withheld for 6 h	2-min inhalation by mouth of 5 to 40 mg/mL acetaldehyde (corresponds to 150 to 1,200 mg/m^3)	Asthmatic group: PC_{20} = 17.55 mg/mL (range 1.96 to 40 mg/mL) corresponds to 527 mg/m^3 acetaldehyde in air No bronchoconstriction was observed in the healthy group.	527
Prieto et al. 2002a	Caucasian asthmatic males and females (n = 16) Asthmatics were not receiving regular medication other than occasional use of β_2-agonists, which were withheld for 6 h	2-min inhalation by mouth of 2.5, 5, 10, 20, 40, and 80 mg/mL acetaldehyde (corresponds to 75, 150, 300, 600, 1,200, and 2,400 mg/m^3)	PC_{20} = 38.9 mg/mL (range 8.4 to 80.0 mg/mL) corresponds to 1,245 mg/m^3 acetaldehyde in air Study participants reported cough (64%), dyspnea (57%), and throat irritation (43%) at the PC_{20} exposure level. When repeated 4–7 d later, the PC_{20} results were moderately repeatable.	1245
Prieto et al. 2002b	Caucasian males and females with allergic rhinitis (n = 43) Caucasian asthmatic males and females (n = 16) Caucasian healthy males and females (n = 19) Asthmatics were not receiving regular medication other than occasional use of β_2-agonists, which were withheld for 8 h	2-min inhalation by mouth of 2.5, 5, 10, 20, 40, and 80 mg/mL acetaldehyde (corresponds to 75, 150, 300, 600, 1,200, and 2,400 mg/m^3)	Allergic rhinitis group: PC_{20} = 67.6 mg/mL (range 15.5 to 80 mg/mL) corresponds to 2,166 mg/m^3 acetaldehyde in air Asthmatic group: PC_{20} = 35.5 mg/mL (range 8.4 to 80 mg/mL) corresponds to 1,136 mg/m^3 acetaldehyde in air No bronchoconstriction was observed in the healthy group.	Allergic rhinitis group: 2166 Asthmatic group: 1136

A3. Epidemiological Studies

Study	Participants	Exposure	Results	NOAEL/LOAEL
Flamant-Hulin et al. 2010	Healthy children (10.3 ± 0.7 y); n = 70 Asthmatic children (10.7 ± 0.7 y); n = 34	Cross-sectional study design Air pollution in classrooms and schoolyards was assessed over a 5-weekday period. FeNO concentration was measured for each participant.	Acetaldehyde concentrations were greater in classrooms than schoolyards. Mean levels in classrooms were 9.3 and 16.4 $\mu g/m^3$, for low and high exposure groups respectively. For schoolyards, the mean levels were 2.4 and 4 $\mu g/m^3$. An increase in FeNO was noted in healthy and asthmatic children in the high exposure group compared to the low exposure group. For classroom exposure, the increase in log(FeNO) was 0.16 (0.07–0.26 95% CI) for healthy children and 0.04 (–0.07 to 0.14 95%CI) for asthmatic children. Within the healthy children, the effect of acetaldehyde was stronger in atopic than non-atopic (p = 0.0081) children.	Not applicable

APPENDIX B: TOXICOLOGICAL STUDIES

B1. Short-term Exposure Studies

Study	Participants	Exposure	Results	NOAEL/LOAEL
Babiuk, Steinhagen and Barrow 1985	Male F344 rats (n = 4/group), 150–180 g	Head-only exposure to a range of acetaldehyde concentrations for 10 min	Sensory irritation measured based on respiratory rate depression RD_{50} = 5,341 mg/m^3	NOAEL/LOAEL not determinable
Cassee et al. 1996	Male Wistar rats (n = 4/group), 240–300 g	Nose-only exposure to 5,000, 8,200 or 11,600 mg/m^3 acetaldehyde for 30 min	Sensory irritation measured based on respiratory rate depression RD_{50} = 5,439 mg/m^3	NOAEL/LOAEL not determinable
Kawano et al. 2012	Female BALB/c mice (n = 8/group), 4–6 wk old	Mice sensitized with mite allergen, then received intranasal acetaldehyde (50 µg)	Increased airway hyperresponsiveness, pulmonary eosinophils, and cytokines in sensitized mice treated with acetaldehyde compared to sensitization-only; no changes in acetaldehyde-only mice	Not applicable; intranasal injection
Lam, Casanova and Heck d'A. 1986	Male F344 rats (group size not provided)	0, 179, 536, 1,786, or 5,357 mg/m^3 acetaldehyde for 6 h or 1,000 mg/m^3 acetaldehyde for 6 h/d × 5 d	Single exposure to 1,786 and 5,357 mg/m^3 increased the DNA in the aqueous-organic interface of rat nasal mucosal homogenates (interfacial DNA) ($p < 0.05$). Increased DNA–protein crosslinking (interfacial DNA) was detected in the olfactory mucosa after repeated exposure at 1,786 mg/m^3, but not after a single exposure.	Single exposure: NOAEL : 536 mg/m^3 LOAEL: 1,786 mg/m^3 Repeated exposure: NOAEL: Not determined LOAEL: 1,786 mg/m^3
Matsuse et al. 2007	Female BALB/c mice (n = 4/group)	Mice sensitized with mite allergen, then received intranasal acetaldehyde (3%, 50 µL)	Increased airway inflammation in sensitized mice exposed to acetaldehyde compared to sensitization only; no inflammation in acetaldehyde-only mice	Not applicable; intranasal injection
Myou et al., 1994a	Male Hartley guinea pigs (n = 6), 350–400 g	0, 31.3, 62.5, 125, and 250 mM nebulized acetaldehyde for 15 s Insufficient information to convert to a concentration in air	Concentration-dependent increase in bronchoconstriction; pre-treatment with diphenhydramine prevented the effect.	NOAEL: 62.5 mM (2.76 mg/mL) LOAEL: 125 mM (5.51 mg/mL) Insufficient information to convert to a concentration in air
Myou et al. 2001	Male Hartley guinea pigs (n = 6), 350–400 g	0, 5, 10, and 20 mg/mL nebulized acetaldehyde for 20 s Insufficient information to convert to a concentration in air	Concentration-dependent increase in bronchoconstriction; pre-treatment with FK224 or capsaicin did not alter the effect.	NOAEL: 2.5 mg/mL LOAEL: 5 mg/mL Insufficient information to convert to a concentration in air

Ortiz, Griffits and Littleton 1974	Male TO mice (n = 10/group), 18–22 g	750 mg/m^3 at start and increased to 4,320 mg/m^3 acetaldehyde over 10 d followed by a recovery period (6 h)	Exposure: Initially, mice had increased excitability (peak at 30 min), followed by locomotor depression, ataxia, and death in 20% on 10th day; increased monoamine neurotransmitter in brain tissue with exposure duration Recovery: Initially, mice exhibited excitation, tremor, piloerection, tail lift, and convulsions for up to 2 h after withdrawal; transient increase in catecholamine in brain tissue; all neurotransmitters to baseline at 6 h	NOAEL/LOAEL not determinable
Stanek et al. 2001	Male F344 rats (n = 3-6/group), 45–70 d old	0, 9, 45, 89, 179, 268, 357, 625, 893 or 5,357 mg/m^3 acetaldehyde for 50 min	Vasodilation in the upper respiratory tract at 45 mg/m^3 and greater; effect observed within 3 min of exposure and capsaicin exposure diminished the response Vasodilation is a common response to irritant gases.	NOEL: 9 mg/m^3 LOEL: 45 mg/m^3 Not considered adverse
Stanek and Morris 1999	Male F344 rats (group size not provided), 45–70 d old	0 or 2,679 mg/m^3 acetaldehyde for 6 h	Exposure did not increase DNA–protein crosslinking in the respiratory mucosa.	NOAEL: 2,679 mg/m^3
Steinhagen and Barrow 1984	Male B6C3F1 (19–27 g) and Swiss-Webster (20–32 g) mice (n = 3–4/group)	Head-only exposure to a range of acetaldehyde concentrations for 10 min	Sensory irritation measured based on respiratory rate depression B6C3F1 mice RD_{50} = 5,236 mg/m^3 Swiss-Webster RD_{50} = 5,080 mg/m^3	NOAEL/LOAEL not determinable

B2. Subchronic and Chronic Exposure Studies

Study	Participants	Exposure	Results	NOAEL/LOAEL
Appelman, Wouterson and Feron 1982	Male and female Wistar rats (n = 10/sex/group), mean weights 191 g (males) and 149 g (females)	0, 714, 1,786, 3,929 or 8,929 mg/m^3 acetaldehyde for 6 h/d × 5 d/wk × 4 wk	Lesions of the olfactory epithelium at all concentrations; lesions of the respiratory epithelium at 1,786 mg/m^3 and higher; lesions of the larynx and trachea at 3,929 and 8,929 mg/m^3 714 mg/m^3: 16/20 olfactory epithelium degeneration; 0/20 respiratory epithelium degeneration; 0/16 larynx epithelium degeneration; 0/18 trachea epithelium degeneration 1,786 mg/m^3: 20/20 olfactory epithelium degeneration; 7/20 respiratory epithelium degeneration; 0/18 larynx epithelium degeneration; 0/18 trachea epithelium degeneration 3,929 mg/m^3: 19/19 olfactory epithelium degeneration; 7/19 respiratory epithelium degeneration; 15/18 larynx epithelium degeneration; 5/16 trachea epithelium degeneration 8,929 mg/m^3: 20/20 olfactory epithelium degeneration; 20/20 respiratory epithelium degeneration; 19/19 larynx epithelium degeneration; 16/17 trachea epithelium degeneration	NOAEL: Not determined LOAEL: 714 mg/m^3
Appelman et al. 1986	Male Wistar rats (n = 10/group), 125–150 g	0, 268, or 893 mg/m^3 acetaldehyde for 6 h/d × 5 d/wk × 4 wk	Lesions of the olfactory epithelium at 893 mg/m^3; no effects at 268 mg/m^3 268 mg/m^3: 0/10 olfactory epithelium degeneration 893 mg/m^3: 10/19 olfactory epithelium degeneration	NOAEL: 268 mg/m^3 LOAEL: 893 mg/m^3
Aranyi et al. 1986	Female CD1 mice (n = 140–193/group), 4–5wk old	0 or 357 mg/m^3 acetaldehyde for 3 h/d × 5 d Following exposure, mice were challenged with inhaled *Klebsiella pneumoniae*	Pulmonary bacteriocidal activity decreased in the exposure group ($p < 0.05$). Exposure did not increase mortality following bacterial challenge.	NOAEL: Not determined LOAEL: 357 mg/m^3
Cassee, Feron and Groten 1996	Male Wistar rats (n = 5/group)	0, 1,339, or 2,679 mg/m^3 acetaldehyde for 6 h/d × 3 d	Concentration-dependent necrosis in the olfactory epithelium Low: 3/5 a few necrotic cells High: 1/5 a few necrotic cells; 2/5 moderate number of necrotic cells; 1/5 many necrotic cells	NOAEL: Not determined LOAEL: 1,339 mg/m^3

Dorman et al. 2008	Male F344 rats (n = 12/group), 8 wk old	0, 89, 268, 893 or 2,679 mg/m^3 acetaldehyde for 6 h/d × 5 d/wk × 13 wk	Concentration-dependent increase in lesions of the olfactory epithelium at 89 mg/m^3 and above; alterations to respiratory epithelium at 268 mg/m^3 and above Exposure was not associated with increased DNA–protein crosslinks. 89 mg/m^3: 0/12 olfactory epithelium degeneration; 0/12 respiratory epithelium degeneration 268 mg/m^3: 12/12 olfactory epithelium degeneration; 1/12 respiratory epithelium degeneration 893 mg/m^3: 12/12 olfactory epithelium degeneration; 11/12 respiratory epithelium degeneration 2,679 mg/m^3: 12/12 olfactory epithelium degeneration; 12/12 respiratory epithelium degeneration	NOAEL: 89 mg/m^3 LOAEL: 268 mg/m^3 Incidence counts in Erratum
Feron 1979	Young male Syrian hamsters (n = 35/group)	0 or 2,679 mg/m^3 acetaldehyde for 7 h/d × 5 d/wk × 52 wk	Marked lesions in the nasal cavity and slight changes in the trachea; a 26-wk recovery period reduced the extent and severity of the lesions No neoplastic lesions were identified.	NOAEL: not determined LOAEL: 2,679 mg/m^3
Feron, Kruysse and Woutersen 1982	Male and female Syrian hamsters (n = 36/sex/group), 8 wk old	0 or 4,464/2,946 mg/m^3 acetaldehyde for 7 h/d × 5 d/wk × 52 wk Highest exposure group reduced in concentration over 9–44 wk due to severity of the effects	Marked lesions of the nasal, tracheal, and laryngeal tissues; no change in lesions after a 26 wk recovery period Neoplastic lesions noted in the nose and larynx Males: 24/27 nasal epithelium lesion; 10/23 laryngeal epithelium lesion; 2/29 nasal tumour; 6/29 laryngeal tumour Females: 21/26 nasal epithelium lesion; 7/20 laryngeal epithelium lesion; 1/29 nasal tumour; 4/29 laryngeal tumour	NOAEL: not determined LOAEL: 4,464/ 2,946 mg/m^3
Kruysse, Feron and Til 1975	Male and female Syrian hamsters (n = 10/sex/group), 72–107 g	0, 696, 2,393, or 8,143 mg/m^3 acetaldehyde for 6 h/d × 5 d/wk × 90 d	Mild lesions of the tracheal epithelium at 2,393 mg/m^3; more severe lesions of the nasal cavity, larynx, trachea, bronchi and lungs at 8,143 mg/m^3 Increased testicle weight at 8,143 mg/m^3; decreased ovary weight at 2,393 mg/m^3	NOAEL: 696 mg/m^3 LOAEL: 2,393 mg/m^3 Incidence counts not provided
Kunugita et al. 2008	Male mice (ALDH2$^{-/-}$ and C57BL/6J wild-type), 12–16 wk old	0, 223, or 893 mg/m^3 acetaldehyde continuously for 14 d	Significant increase in micronucleus frequencies in reticulocytes and TCR gene mutations in T-lymphocytes in ALDH2$^{-/-}$ but not wild-type mice following 223 mg/m^3 and 893 mg/m^3 acetaldehyde exposure.	NOAEL: Not determined LOAEL: 223 mg/m^3

Lacroix et al. 2002	Male Hartley guinea pigs (n = 8/group), 4 wk old	0 or 0.4 mg/m^3 acetaldehyde for 6 h/d × 5 d/wk × 4 wk Half of the guinea pigs were sensitized with ovalbumin	Acetaldehyde exposure caused slight irritation of the respiratory epithelium in both groups of animals. Exposure did not alter respiratory function parameters or allergic responses the sensitized group compared to sensitization alone.	NOAEL: Not determined LOAEL: 0.4 mg/m^3
Ogawa et al. 2006	Mice (ALDH2$^{-/-}$ and C57BL/6J wild-type), 16 wk old	Continuous exposure to 223 or 893 mg/m^3 acetaldehyde for 14 d	At 223 mg/m^3, no increase in urinary 8-OHdG was observed. At 893 mg/m^3, an increase in urinary 8-OHdG was observed at 6 and 12 d of exposure ($p < 0.01$); no strain effect was observed. Plasma levels of malondialdehyde were unchanged in the study.	NOAEL: Not determined LOAEL: 223 mg/m^3
Oyama et al. 2007	Male ALDH2$^{-/-}$ and wild-type mice (n = 4–5/group), 10 wk old	0, 223, or 893 mg/m^3 acetaldehyde for 24 h/d × 14 d	Concentration-dependent histological lesions of the nasal cavity, larynx, pharynx, and trachea; greater effects observed in ALDH2$^{-/-}$ mice Wild-type Low: 2/4 respiratory epithelium degeneration; 0/4 olfactory degeneration; 0/4 nasal subepithelium hemorrhage; 0/4 respiratory epithelium degeneration in the larynx/pharynx/trachea Wild-type High: 3/5 respiratory epithelium degeneration; 1/5 olfactory degeneration; 0/5 nasal subepithelium hemorrhage; 0/5 respiratory epithelium degeneration in the larynx/pharynx/trachea Knockout Low: 3/4 respiratory epithelium degeneration; 0/4 olfactory degeneration; 2/4 nasal subepithelium hemorrhage; 3/4 respiratory epithelium degeneration in the larynx/pharynx/trachea Knockout High: 4/5 respiratory epithelium degeneration; 1/5 olfactory degeneration; 4/5 nasal subepithelium hemorrhage; 4/5 respiratory epithelium degeneration in the larynx/pharynx/trachea	NOAEL: Not determined LOAEL: 223 mg/m^3

Oyama et al. 2010	Mice ($ALDH2^{-/-}$ and C57BL/6J wild-type), 10 wk old	Continuous exposure to 223 or 893 mg/m^3 acetaldehyde for 14 d	DNA adducts were detected in nasal tissue from $ALDH2^{-/-}$ mice; however, whether acetaldehyde increased the adducts cannot be determined, as results from the nasal tissues of controls and 893 mg/m^3 groups were not published. At 223 mg/m^3 acetaldehyde, adducts were higher in knockout than wild-type mice ($p < 0.05$). An increase in levels of DNA adducts in lung tissue and dorsal skin was also noted with acetaldehyde exposure, with greater effects in the knockout strain ($p < 0.05$). No significant effects of strain or exposure were noted in adducts of liver tissue. Comparing tissues, the greatest level of adducts was identified in the nasal epithelium ($p < 0.01$).	NOAEL: Not determined LOAEL: 223 mg/m^3
Saldiva et al. 1985	Male Wistar rats (n = 12/group), mean weight 195 g	0 or 434 mg/m^3 acetaldehyde for 8 h/d × 5 d/wk × 5 wk	Inflammatory response in the nasal cavities, including hyperplasia of the olfactory epithelium and inflammatory cell infiltrate in the submucosa; changes in pulmonary mechanics may have been the result of mechanical damage during testing.	NOAEL: Not determined LOAEL: 434 mg/m^3
Shiohara et al. 1985	Male Sprague-Dawley rats (n = 6/group), mean weight 250 g	0 or 0.3 mM acetaldehyde in air for (20 min × 4)/d for 2–21 wk (corresponds to 0 or 13 mg/m^3)	Increased activity of Na^+, K^+-ATPase in the synaptosomal plasma membrane fraction and microsomal fraction of cerebral cortex tissue	NOAEL: Not determined LOEL: 13 mg/m^3 Effect may be due to interaction with plasma membrane and not direct effect on transport enzyme.

Woutersen et al. 1984, 1986; Woutersen and Feron 1987	Male and female Wistar rats (n = 105/sex/group)	0, 1,339, 2,679 or 5,357/1,786 mg/m^3 acetaldehyde for 6 h/d × 5 d/wk × 28 mo Highest exposure group reduced in concentration over 15 mo due to severity of effects in the exposure group	Alterations to olfactory epithelium noted at all exposure levels; alterations to respiratory epithelium and larynx at 2,679 and 5,357/1,786 mg/m^3; rhinitis and sinusitis at 5,357/1,786 mg/m^3. Following 52-wk exposure and 52-wk recovery period, some regeneration of the olfactory epithelium was observed in the 1,339 and 2,679 mg/m^3 groups. Nasal tumour incidence: Males Control:1/49 squamous cell carcinoma; 0/49 adenocarcinoma Males Low: 1/52 squamous cell carcinoma; 16/52 adenocarcinoma Males Medium: 10/53 squamous cell carcinoma; 31/53 adenocarcinoma Males High: 16/49 squamous cell carcinoma; 21/49 adenocarcinoma Females Control: 0/50 squamous cell carcinoma; 0/50 adenocarcinoma Females Low: 0/48 squamous cell carcinoma; 6/48 adenocarcinoma Females Medium: 5/53 squamous cell carcinoma; 28/53 adenocarcinoma Females High: 17/53 squamous cell carcinoma; 23/53 adenocarcinoma	NOAEL: Not determined LOAEL: 1,339 mg/m^3

APPENDIX C: OTHER GUIDELINES AND ASSESSMENTS

C1. Exposure guidelines for short-term exposure

In the Government of Canada's *Priority Substances List Assessment Report: Acetaldehyde*, no guideline for short-term exposure to acetaldehyde was derived (Environment Canada and Health Canada 2000).

For acute exposures, the California EPA (2008) derived an acute reference exposure level of 470 µg/m^3 for a one-hour timeframe, based on the lower limit of the PC_{20} confidence interval (142 mg/m^3) from a study of bronchoconstriction in asthmatic subjects (Prieto et al. 2000). Uncertainty factors of 10 for LOAEL to NOAEL extrapolation, and 30 for asthma exacerbation in children and increased sensitivity to methacholine were applied, for a total UF of 300.

The U.S. EPA (2008) derived an acute exposure guideline limit (AEGL) of 45 ppm (81 mg/m^3) for non-disabling effects for timeframes of 10 minutes to 8 hours, based on the human exposure study by Sim and Pattle (1957) reporting mild upper airway irritation without eye irritation at 134 ppm (239 mg/m^3) acetaldehyde for 30 minutes. A UF of 3 was applied to account for intraspecies variability.

The WHO (1995) derived a TC for irritancy in humans of 2 mg/m^3, based on the NOAEL of 45 mg/m^3 for irritation in human volunteers (Silverman, Schulte and First 1946). Uncertainty factors of 10 for intraspecies variation and 2 for poor data quality were applied, for a total UF of 20.

ANSES (2014) derived a short-term exposure guideline of 3 mg/m^3 for a one-hour timeframe, also based on the lower limit of the PC_{20} confidence interval (142 mg/m^3; 79 ppm) from a study of bronchoconstriction in asthmatic subjects (Prieto et al. 2000). Uncertainty factors of 5 for LOAEL to NOAEL extrapolation, 3 for interindividual variability, and 3 for database uncertainties (owing to the uncertainties associated with translating nebulizer exposure concentrations to air concentrations) were applied, for a total UF of 45.

Table C1. Short-term exposure guidelines from previous assessments

Organization	Exposure guideline	Health effect
CalEPA (2008)	470 µg/m^3 (1 h)	Bronchoconstriction
U.S. EPA (2008)	81 000 µg/m^3 (81 mg/m^3) (10 min to 8 h)	Upper airway irritation
WHO (1995)	2000 µg/m^3 (2 mg/m^3)	Irritation
ANSES (2014)	3000 µg/m^3 (3 mg/m^3) (1 h)	Bronchoconstriction

C2. Exposure guidelines for non-neoplastic chronic effects

Previous assessments have developed guideline values for chronic or long-term acetaldehyde exposure based on degeneration of the olfactory epithelium in rats. For this effect, the subchronic exposure studies in rats by Appelman et al. (1982, 1986) were used as the basis for guideline derivation.

The Government of Canada (Environment Canada and Health Canada 2000) derived a TC of 390 μg/m^3 for non-neoplastic chronic effects. From the Appelman studies (1982, 1986), a lower 95% confidence limit for the benchmark concentration ($BMCL_{05}$) of 218 mg/m^3 was determined and adjusted for continuous exposure (6 hours/24 hours × 5 days/7 days). Uncertainty factors of 10 for interspecies variation and 10 for intraspecies variation were applied, for a total UF of 100.

Using the same studies, the U.S. EPA (1991) derived an inhalation RfC of 9 μg/m^3, based on a NOAEL of 273 mg/m^3 (150 ppm) adjusted for continuous exposure (6 hours/24 hours × 5 days/7 days); an HEC was then calculated using a regional gas dose ratio conversion factor of 0.18 for the extra-thoracic region (HEC = 8.7 mg/m^3). This ratio accounts for pharmacokinetic but not pharmacodynamic differences between animals and humans. Uncertainty factors of 10 for sensitive human populations, 10 to account for subchronic to chronic extrapolation, and 10 to account for interspecies extrapolation and incompleteness of the database were applied, for a total UF of 1000.

The California EPA (2008) derived a chronic reference exposure level of 140 μg/m^3. From the Appelman studies (1982, 1986), a BMC_{05} of 178 mg/m^3 was determined. A dosimetric adjustment factor of 1.36 was applied based on the PBPK model of Teeguarden et al. (2008), and the HEC was adjusted for continuous exposure (6 hours/24 hours × 5 days/7 days). Uncertainty factors of $10^{0.5}$ for subchronic to chronic extrapolation, $10^{0.5}$ for toxicodynamic differences, $10^{0.5}$ for human interindividual toxicokinetic variation, and 10 for human toxicodynamic variation (potential asthma exacerbation in children) were applied, for a total UF of 300.

ANSES (2014) derived a long-term exposure guideline of 160 μg/m^3, based on a NOAEL of 90 mg/m^3 observed in a 13-week rat study (Dorman et al. 2008). Uncertainty factors of 2.5 for toxicodynamic differences and residual uncertainties, 10 for human variability and sensitive subpopulations, and 3 for use of a subchronic study were applied, for a total UF of 75.

Table C2. Exposure guidelines for non-neoplastic effects from previous assessments

Organization	Exposure guideline (μg/m^3)	Health effect
Environment Canada and Health Canada (2000)	390	degeneration of the olfactory epithelium
U.S. EPA (1991)	9	degeneration of the olfactory epithelium
CalEPA (2008)	140	degeneration of the olfactory epithelium
ANSES (2014)	160	degeneration of the olfactory epithelium

C3. Assessments of carcinogenicity

As discussed previously in section 5.1.3, IARC classified acetaldehyde as a Group 2B carcinogen (i.e., possibly carcinogenic to humans) in 1999 and determined in 2012 that there was sufficient evidence in humans for carcinogenicity associated with the consumption of alcoholic beverages. However, this subsequent monograph did not address carcinogenicity associated with acetaldehyde inhalation.

Quantification of cancer risk in most previous assessments has been based on development of nasal tumours (squamous cell carcinomas and adenocarcinomas) in male rats in a carcinogenicity study reported by Woutersen et al. (1984, 1986) . The high-concentration group was excluded from analysis since the exposure level was decreased over the course of the study due to growth retardation, respiratory distress, weight loss, and mortality at the initial exposure concentration.

The Government of Canada (Environment Canada and Health Canada 2000) used a linear multistage model with adjustment for continuous exposures to calculate a tumourigenic potency (TC_{05} representing a 5% increased risk of cancer incidence) of 86 mg/m^3. The corresponding unit risk is 5.8×10^{-7} (μg/m^3)$^{-1}$, and 17.2 μg/m^3 represent the 1 in 100,000 risk level. This value has been revised in this assessment based on new information related to the MOA, as discussed in section 5.4.

The U.S. EPA (1987) classified acetaldehyde as a Group B2, probable human carcinogen, noting that epidemiological evidence was inadequate for assessment of carcinogenicity in humans. A linearized multistage model was used to derive an upper limit unit risk of 2.2×10^{-6} (μg/m^3)$^{-1}$ for a lifetime continuous inhalation exposure. The corresponding 1 in 100,000 risk level is 4.5 μg/m^3.

California EPA's Office of Environmental Health and Hazard Assessment (1993) used a linearized multistage model with different interspecies scaling factors and estimated a range of upper limit unit risk values of 0.54×10^{-6} to 15×10^{-6} (μg/m^3)$^{-1}$. From this range, 2.7×10^{-6} (μg/m^3)$^{-1}$ was determined to be the best estimate, and 3.7 μg/m^3 represents the 1 in 100,000 risk level.

The WHO (1995) utilized both non-linear and linear approaches for its guidance on carcinogenicity of acetaldehyde, given the uncertainty in the mechanism of tumour development. For the non-linear approach, irritation in the upper airway tract was considered necessary for tumour induction, and a TC of 300 μg/m^3 was determined. This was derived from the NOAEL of 275 mg/m^3 for irritation in rats in a 4-week study (Appelman et al. 1986). Uncertainty factors of 10 for interspecies variation, 10 for intraspecies variation, and 10 for study duration and severity of effect were applied, for a total UF of 1000. For the linear approach, cancer risk was estimated using the default linearized multistage approach from Woutersen et al.'s (1986) carcinogenicity study. Concentrations associated with a 10^{-5} increase in cancer risk (1 in 100,000 risk level) ranged from 11 to 65 μg/m^3, which is associated with a unit risk of 1.5×10^{-7} to 9.1×10^{-7} (μg/m^3)$^{-1}$.

Note that ANSES (2014) did not derive an exposure guideline for the carcinogenic effects of acetaldehyde. In their assessment, they state that since olfactory degeneration (the endpoint on which their long-term exposure guideline is based) is a precursor for cancer, protection against non-cancer effects will also permit protection against cancer.

Table C3. Exposure guidelines for neoplastic effects from previous assessments

Organization	Concentration			
	TC $\mu g/m^3$	TC_{05} $\mu g/m^3$	Unit risk $(\mu g/m^3)^{-1}$	$\mu g/m^3$ per 1×10^{-5} risk
Environment Canada and Health Canada (2000)		86,000	5.8×10^{-7}	17.2
U.S. EPA (1987)			2.2×10^{-6}	4.5
CalEPA (1993)			2.7×10^{-6}	3.7
WHO (1995)	300		1.5×10^{-7} to 9.1×10^{-7}	11 to 65